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# THE UNIVERSITY OF TORONTO MEDICAL JOURNAL

(An Undergraduate Publication)

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**Address all communications to Room 107, Anatomy Building.**

**Vol. XIV Toronto, January, 1937 No. 3**


"Sir:

"As undergraduates 'enrolled in the Faculty of Medicine' and being each 'required to pay the annual fee of three dollars to the Bursar,' of which $1.50 is the regular Medical Society fee, some 3rd B. and M. students would like to know why they have not been receiving your 'Medical Journal' according to clause (e), p. 99 of the Calendar . . .

". . . Having paid up our subscription, we look for early forwarding of back and of future issues of this year."

Such is an extract from a letter of December 8, 1936, to the Secretary of the Medical Society, signed by a III B and M. student.

Dear writer, consult said clause (e), p. 99 of the Calendar of the Faculty of Medicine, 1936-37, dealing with the Medical Society. Note that, while the publication of a "Medical Journal" is listed as one of the objects of the Medical Society, there is no statement to the effect that the Medical Society fee of $1.50 (as distinct from that of the Medical Athletic Society fee of $1.50) covers such subscription—any more than this fee covers one's attendance at the Medical "At Home," the promotion of which is also a function of the Society (clause c). This is made clear in the runner enclosed in the Calendar.

Moreover, students in the combined course, although paying the full Arts fees, pay only a portion, large though it may be, of the fees of Second and

Third Years in Medicine during their Third and Fourth Years in Biological and Medical Sciences. In the full sense of the word, they are not enrolled as undergraduates in the Faculty of Medicine.

Again—students enrolled in Biological and Medical Sciences, do not and never have paid the Medical Society fee.

Although such statements as quoted are rather unwarranted, and quite without foundation, this letter merits further consideration. It betokens the unfortunate misunderstanding between Medical undergraduates and students in the Arts course of Biological and Medical Sciences. This misunderstanding is due to a desire on the part of B. and M. students to be a part of the Medical student body during their undergraduate days in Arts—and unfortunate in that it savours of a certain feeling of rivalry between students in Medicine and B. and M.

In order to more fully understand the problem facing the student who brought this matter to our attention, we must consider students in the Combined Course during two periods in their training. The first is as an undergraduate in Arts in the thrid and fourth years of his course. The second is as an undergraduate in the clinical years in Medicine.

During the former period, they are full-fledged and paid-up members of an Arts college's undergraduate organization. They associate intimately extra-curricularly with Arts students in courses much less arduous and exacting of time than their's. They attend, however, very few College lectures. If it were not for the higher requirements exacted in examinations in May, there would be little to convince such a student that he was not in Medicine. They attend practically the same lectures, in the same building (and the Medical Building at that), by the same professors; listen to the same election speeches, yet are unable to run for office or vote. That there is an academic bond between the two courses is the fact that students in B. and M., who are just below the line, are favoured with the privilege of passing into the following year of the Medical course.

Although having the opportunities to associate freely with Medical undergraduates, during this period they can take no part in Medical activities, for they do not pay the Medical Society or Class fees. A final year student in B. and M. is unable to run for any office offered that year in the Medical undergraduate organization, although the duties of such office would not commence until he were a member of a Medical class and the Medical Society.

During the second period, the graduate in B. and M. becomes an undergraduate in the clinical years in Medicine. He now wishes to take an active part in undergraduate activities, but is hampered by absence of previous associations in these and a certain feeling that, some way or another, he is not a tried member of the Medical undergraduate body.

Now that the reduced subscription rates to the Journal has been added to the Medical Society fee, the staff of the Journal is confronted with two problems.

Firstly, they are desirous of distributing the Journal to B. and M. students at the reduced rate available to Medical undergraduates. This is not constitutional and is financially impractical if a commission is to be paid to a subscription agent.

Secondly, the inclusion on the staff of the Journal of an Assistant Editor from IV. B. and M. is a constitutional requirement. Such a student is a staff member of an organization now completely within the Medical Society, yet he is not a member of that Society.

In order to iron out ill-feelings and practical difficulties, which insufficiently close association of these two courses presents, a movement is afoot to obtain closer and more friendly co-operation between the student bodies. As this goes forward, the support and advice of undergraduates on both sides of the issue is asked.

# TECHNICAL DETAILS OF RADICAL EXCISION OF ULCER OF LEG

By STUART GORDON, M.S. (Tor.)

Two papers appearing in earlier issues of this journal have outlined the modern view regarding the surgical pathology of recurrent leg ulceration. Based on this conception of the fundamental faults the operative technique detailed below has been suggested.

As has been previously explained, radical excision for recurrent leg ulceration is only carried out after all ulceration has healed. This is the first important point in the successful surgical handling of the disease. It is believed that the basic fault is a slowly progressive lymphatic obstruction in the subcutaneous tissues, external to the deep fascia. This has been started off by infection, and has remained outside the deep fascia because of the absence of anastomoses between the deep and superficial lymphatics. It is not our desire to introduce infection into the deep lymphatics, otherwise the end result will not be all that we wish it. Therefore operation is delayed until complete healing has occurred.

Once the leg is healed operation may be proceeded with. Any general anaesthetic may be used. A sterile preparation is done on the day prior to operation. This consists of shaving the leg from hip to toes. The limb is washed with soap and water, cleansed with alcohol, and wrapped in sterile towels until the time of operation.

After the patient has been anaesthetized the wrappings are removed from the leg and the leg is prepared. Iodine is painted on the skin. After it has dried it is washed off with alcohol. The operative area is draped off with sterile sheets.

An incision is made the length of the inner side of the leg. This is carried down to the deep fascia. The skin edges are undercut. Fascia is then excised, a strip about 1½ inches wide and the length of the leg, being removed. The area of skin previously ulcerated is excised together with its underlying tissue. The incision, down to the area of excision is sewn.

A Thiersch—or split—graft is cut from the thigh. It is an advantage to get this in one piece if possible. Many small pieces of graft prolong the operative time. The overlapping necessary to cover the raw area with multiple grifts means more bits of dead skin to separate later, or to serve as a nidus for infection. To obtain a large graft three things are necessary—(1) practice, (2) a sharp knife, and (3) some device for keeping the skin surface flat ahead of the knife.

The bed of the graft should be dry. All bleeders are tied with fine catgut in order that a minimum of foreign material should lie under the graft. The latter is spread over its new bed smoothly and evenly. It is sutured to the edge of the defect and also to its bed. This prevents slipping. Finally many small punctures are made in the graft. These allow any serum, etc., which may collect under the graft, and so separate it from its bed, to escape without causing any trouble.

A soft, smooth, voluminous dressing is applied over the graft. This is held in place by a flannelette bandage firmly applied. A moderate, even pressure over the graft is one of the essentials for a successful take. Lastly, the leg and foot are encased in a light splint to keep movement at a minimum

Ten days later all dressings are removed and stitches carefully taken out.

If a complete "take" has been obtained, a dressing of sterile paraffin oil is applied. The graft is exposed to the air for two hours a day; the time slowly being increased until no dress-

ing is required. Should there be one or two areas of incomplete "take" weak hygeol dressings are used at regular intervals until no longer required.

No patient is discharged until the leg is completely healed. For the next three months a crepe bandage is worn during the day. This serves a dual purpose, supporting and aiding of the lymphatic circulation and protection from minor traumata.

This operation was first suggested by Homans some years ago. We feel that the technique is a valuable one, and one justifying a much wider adoption than it at present enjoys.

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## FUNDUS MANIFESTATIONS IN METABOLIC DISEASES *

By WALTER R. CAMPBELL, M.A., M.D., F.R.C.P. (C.), Toronto

The changes occurring in the fundus oculi have a distinct value in the diagnosis and prognosis of certain diseases. To the neurologist, fundus examination is, of course, invaluable, but to those working in the field of general medicine, the ability to recognize five types of fundi is of particular importance. The first, of course, is the normal fundus; the second, the arteriosclerotic fundus; the third, the diabetic fundus; the fourth, the nephritic fundus; and, last, the fundus of malignant hypertension. Naturally, it is desirable to be able to differentiate these pictures one from another and also from other diseases of the eye. Of greatest importance, however, is the ability to recognize that the fundus is abnormal or unusual, thereby recognizing the necessity for calling on a trained ophthalmologist for assistance. Important as it is, I do not intend to describe the normal fundus, but merely to notice some of the abnormalities as they occur in these cases. Among these, I have placed the arteriosclerotic fundus first, since it is the simplest and is also encountered in its various forms in other conditions.

Many of us are apt to be discouraged with our slow progress in ophthalmoscopy. With modern instruments, the difficulty is not so much due to technique as to the supposed dearth of suitable patients. In point of fact, there is no dearth. The more fundi of normal individuals one can examine, the better is one prepared to recognize the abnormal fundus. As to the abnormal, they are not less frequent here than elsewhere in the world and diligent search for them brings its reward. A careful and complete examination of the retina can scarcely be made without dilatation of the pupil with a mydriatic. Particularly in the aged with shallow anterior chambers, the danger of subsequent glaucoma should be avoided by instilling a drop of one-half per cent. eserin solution in the conjunctival sac after examination.

Text-books usually describe first the optic disc. In this group of cases, the disc or papilla is of lesser importance than some other structures in the fundus, such as the vessels. By direct ophthalmoscopy, the fundus is magnified some fifteen times. Have the patient fix his eye on a point, and by moving slightly, if necessary, a vessel comes into view. These vessels are similarly magnified, so that we have here an opportunity of observing comparatively small vessels, vessels much smaller than any we can palpate, and at the same time much nearer to the actual distributors of nutrition to the body cells, the capillary vessels. As Moore has pointed out, these vessels are not normally subject to the large variations in pressure that obtain in other larger vessels. The blood flow is more continuous than

* By kind permission of Editor, Canadian Medical Association Journal.

rhythmic, and pulsation is noted only under exceptional circumstances. The retinal vessels are located in the inner, cerebral, or nerve fibre layer of the retina. Veins are about one and one-half times the diameter of the accompanying arteries, appear somewhat less cylindrical than arteries, are darker in colour and rarely possess as marked a light streak unless abnormal. In the albinotic and in the tesselated fundus, indications of choroidal blood vessels are seen in the form of red flat ribbons extending apparently without pattern across the field. It is impossible to differentiate the choroidal artery from the choroidal vein.

Tracing the retinal vessels toward the disc, there may be several features worthy of note in arteriosclerosis. It is sometimes thought that tortuosity is one of the most important of these, but, as a matter of fact, the large individual variations in tortuosity of normal vessels make the diagnosis somewhat difficult. When, in an œdematous retina, the vessels are seen to weave into and out of focus by assuming different depths in the inner retinal layer as well as a distinctly tortuous course over the fundus, and also when the macular arteries are seen to pursue a course resembling a corkscrew, tortuosity may be diagnosed by the least experienced, but much experience is necessary to identify the less pronounced cases of tortuosity.

The size of the vessels is of considerable importance in differentiating various fundus conditions. In simple arteriosclerosis, the size of the veins is not changed from normal, nor is the size of the artery consistently changed. In speaking of the size of the vessel, however, it must be remembered that the normal vessel is perfectly transparent and, therefore, invisible. What we really see is the size of the blood column. When, however, a thickening of the intima occurs, it is usually somewhat patchy in character and this is shown by a contraction of the blood column alternating with regions where its width is normal. This is characteristic of an *intimal* sclerosis of considerable severity. The light streak on the artery is normally about one-fourth the width of the artery. With the development of a *medial* sclerosis, this becomes wider and assumes a burnished copper appearance and sometimes appears to be finely beaded. Considerable care must be exercised in the interpretation of this sign, as it is only an exaggeration of the normal and is somewhat dependent on the amount and quality of the light used, but, when well marked, it may be regarded as definitely pathological. In essential hypertension, it is only seen in the severe or late stage of the disease. Distinct perivasculitis is seldom seen in the simple arteriosclerotic fundus.

Some of the most important signs of vascular sclerosis are to be found where arteries and veins cross. Ofter the vein is faintly visible through the normal artery wall, and it is, of course, visible right up to the arterial stream. In arteriosclerosis, the vein becomes invisible for some little distance from the arterial blood column due to the increase in the thickness of the artery wall. Accompanying the more severe degrees of arterial change, there is also a distinct change in direction of the vein as it is crossed by the artery. While the usual course of the vessels may make acute angles at the crossing, one sometimes sees the vein turn sharply to pass under (or over) the artery at a right angle, then turn back to continue the original direction. Dilation of the veins distal to the point of crossing may be observed. It is due to local mechanical causes, and its significance is quite different from that of a generalized dilatation of veins which accompanies papilloedema from any cause.

Tracing down the vessels, one comes upon the disc. Careful examination of the disc should be made for colour, the condition of its margin, the level, and the vessels. In simple arteriosclerosis, apart from the changes which may occur in the vessels, there is slight, if any, abnormality of the papilla. Four principal arteries with the accompanying veins

pass out from the papilla and each of these should be examined in turn for the foregoing evidences of vascular sclerosis. In addition, the sector of the retina through which the vessel courses should be searched for other abnormal findings, such as œdema or white areas, and particularly the macular region should be examined for a macular star—partial or complete. These appearances should not be present in the simple arteriosclerotic fundus, nor are hæmorrhages, though frequently present a necessary feature of this condition. They seem more likely to be present if high blood pressure accompanies the arteriosclerosis and are commonly superficial and flame shaped, though round punctate hæmorrhages in the deeper layers of the retina also occur. Chorioretinitis is sometimes seen in simple arteriosclerosis, though it also accompanies syphilis, tuberculosis and nephritis. Pigmentation and depigmentation, alone or intermingled with white areas representting complete sclerosis of the vessels of the choroid, or white areas with red ribbons representing their partial sclerosis, are to be found in the fundus deep to the retinal vessels. In arteriosclerosis, the macular and the peripapillary are the most frequently affected, but the degree of injury is seldom as great as with syphilis or even nephritis.

I have described, at some length, the characteristic features of the simple arteriosclerotic fundus. These features are found in varying degree in the fundi to be later described, or, in other words, the peculiarities of these fundi are usually engrafted on a basis of arteriosclerosis or raised blood pressure or both. Diabetics frequently have ocular abnormalities, many of them more interesting than the fundus changes, but these cannot be discussed here The fundus changes of diabetics never occur in the young and have no relation to severity, and the diabetes is of some considerable duration when they become recognizable. It is equally true, however, that diabetes of long standing may be present without any gross alterations in the fundus other than those of simple arteriosclerosis.

While the diabetic fundus has some points of resemblance to that of other conditions, certain points are rather distinctive. Fine, rounded, yellowish-white solid masses with sharp edges, sometimes confluent, may occur between papilla and macula and surrounding the macula. Hæmorrhage and hypertension are absent. The disc is normal. There is never a macular star. In cases of greater severity, hæmorrhages of varying size appear, and in the most severe cases, a retinal exudate and papillœdema are present, which is difficult to differentiate from those of renal injury, since raised blood pressure and albuminuria are also present at this stage. The earlier degrees are susceptible to dietetic and insulin treatment. The more severe degrees are not, though I am not prepared to agree with Grafe that they constitute a contra-indication to insulin treatment of a diabetic patient.

The picture in diabetic lipæmia is an unusual and exceedingly characteristic one. The eye-ground as a whole is pale as in an anæmia, with a peculiar fluorescence, but the blood vessels are unique. The artery and vein are the same colour and this colour is creamy white at the vessel margins, particularly in the periphery of the fundus, with an increasing amount of red tint toward the midline of the vessel. As the fat appears to collect along the vessel wall and even to infiltrate it, one continues to find the sign present when drawn blood no longer shows evidence of lipæmia microscopically. Approximately six per cent. of fat must be present in blood before the lipæmic fundus is recognizable as such. No changes appear in the disc. The condition occurs only in the young and only during diabetic acidosis or coma. The administration of insulin rapidly abolishes all evidence of lipæmia and the lipæmic fundus soon returns to normal. The sweet odour of acetone, or other signs of acidosis, invariably accompany the lipæmic fundus and there is little, if any, danger of confusion with the retinitis of leukæmia, which differs also in showing papillary and peripapillary

œdema, hæmorrhages, and often broad white lines alongside the vessels.

It has been previously indicated that the fundus lesions of renal disease are associated with evidences of arteriosclerosis. While this is in the main true, certain qualifications should be noted. In degenerative kidney lesions or nephroses, no fundus charges are found. The focal nephritides, such as may be encountered in subacute bacterial endocarditis, puerperal infections, etc.. sometimes show a few white areas of degeneration and hæmorrhages, usually with a white centre. In not more than ten per cent. of cases of acute diffuse glomerulonephritis, a papillœdema and retinitis, with cotton wool exudates and hæmorrhages, may occur in the retina. These heal completely. Chorioretinitis and the macular star are absent. In the subchronic stage of nephritis (parenchymatous nephritis) seldom are eyeground changes seen, unless the blood pressure is unusually high. Hæmorrhages, a retinal œdema, and rarely a papillœdema may occur.

The fundus changes in the nephritis of pregnancy may be particularly severe and often permanent. They are similar to the changes seen in acute glomerulonephritis, but, as a rule, more extensive. The arteries are often contracted and a neuritic atrophy may follow. The grade of œdema may be so great as to produce a detachment of the retina, and chorioretinitis with pigmentation may occur. The prognosis in retinal detachment in these cases as opposed to that occurring in rare cases of acute glomerulonephritis is not wholly bad. Re-attachment is sometimes seen, but if this does not occur soon, further degenerative changes are inevitable and vision may be much reduced, especially if the macular area is involved. Therapeutic abortion or induction of premature labour must be carefully considered. Since the retinitis usually occurs in the later months of pregnancy, a viable child is to be expected. If early fundus changes only are present, these may be favourably influenced by such procedures, but late changes are not. Other eye diseases, especially the fundus changes of a chronic nephritis, are unfavourably influenced by pregnancy, and therapeutic abortion is indicated not only from the ocular, but also from the renal standpoint. As to the likelihood of recurrency of retinitis in subsequent pregnancies, opinion is divided. It now seems probable from recent evidence that the renal injury will recur in perhaps seven out of ten cases and in some of these fundus changes may be expected to develop. Such patients should be advised against pregnancy.

In chronic glomerulonephritis, the development of retinal changes is of evil omen, indicating as it usually does death within one or two years. Many have thought that the retinal vascular sclerosis in chronic nephritis is secondary to the retinitis. This is, however, wholly contrary to the history of renal disease, and from a pathological standpoint, must be regarded as improbable. There can be little doubt, however, that the advance is rapid following the development of a retinitis. Due to the associated anæmia, the disc, as well as the fundus generally, is pale. Papillœdema is rare; cotton wool exudates are rare; but dense white snow banks may surround the disc and appear elsewhere in the fundus. Absorption of these takes place, leaving fine white dots in the retina which, in the macular region, tend to arrange themselves in a star-shaped or fan-like manner. Flame-shaped hæmorrhages occur in the nerve fibre layer, and exudate and hæmorrhages in the deeper layers of the retina, and later varying degrees of chorioretinitis with exudates, pigmentation and depigmentation appear. With such changes in the fundus, an advanced degree of renal insufficiency is present. Indeed, it would appear that renal insufficiency is an essential feature in the development of this picture, since it also appears in the late stages of the subacute progressive form where vascular changes are not so marked, but renal insufficiency is an outstanding feature of the patient's condition.

Closely allied to the fundus changes of chronic nephritis are those described

by Keith and Wagener in malignant hypertension, or by Foster Moore as arteriosclerosis retinitis, and from the renal viewpoint by Volhard and Fahr in the so-called "combination form" of arteriosclerosis plus nephritis. Keith's work, however, goes to show that the injury is more widespread than a vasculorenal disease and that such patients may suffer more from the cerebral and cardiac complications than the renal element. Proof that a patient with a typical fundus has a satisfactory renal function is not to be taken as indicating a good prognosis, as such patients usually die in a relatively short time of other causes —cerebral or cardiac failure—or, more typically, of a simultaneous failure of all three. In the fundi, the arteries are strongly contracted; arteriosclerosis is always a prominent feature; the retinitis consists at first of a papillary hyperæmia and mild œdema with a few papillary cotton wool exudates and hæmorrhages. Intimal sclerosis is rare. With greater severity, the area of the serous papillary œdema extends outwards involving the macula. Exudates are still of the cotton wool variety. Later, the hyperæmia of the disc fades, the œdematous area recedes from the periphery, punctate exudates appear, and a fine macular star develops. Vascular sclerosis becomes more marked; perivasculitis appears, denoted by the silver wire artery and the white lines beside the blood column of both artery and vein. In the last stage, secondary optic atrophy, macular star, punctate exudates, a few hæmorrhages, and marked retinal arteriosclerosis and chorioretinitis are present. Vision is of course, reduced. This final stage is seldom observed, as the patients usually die in the preceding stages. This picture differs from that of chronic nephritis in the contraction of the arteries, the degree of sclerosis, the well-marked hyperæmia of the disc and the papillœdema, and the absence of the peripapillary snowbanks of nephritis, together with the clinical evidence obtained from the history and physical examination of the patient.

Few other metabolic diseases show characteristic fundus changes. In hyperthyroidism, pulsation of the retinal arteries at a distance from the papilla occurs. Aortic regurgitation, intracranial or intraocular tumour, and glaucoma must be excluded. As the sign is not constant and is only present in well-marked cases of the disease, it is seldom used. Coupled with an arterial flash seen extending to the finger-tips on their transillumination, it is, in the absence of aortic regurgitation, as highly diagnostic as the estimation of the basal metabolic rate, though it cannot be used in a quantitative manner.

A question may be asked: Are these fundus changes diagnostic? Can one by this means recognize the disease causing the injury? The answer is: sometimes; with increasing skill, more often. It should be pointed out, however, that we seldom make a diagnosis on a single observation, and the recognition of these abnormalities in the fundus should initiate an investigation calculated to uncover their cause. When this is discovered, the state of the fundus gives useful information and no mean help in many instances as to the probable outcome of the case, not alone from the standpoint of the opthalmologist, but also from that of the internist.

# MODERN CONCEPTIONS OF CONTRACTION AND DISPROPORTION OF THE FEMALE PELVIS*

By JOHN L. CATHIE, '37

A pelvis is regarded as contracted when any of its essential diameters are so shortened as to affect materially the normal mechanism of labour, whether or not the ultimate delivery of the child is impeded. Deformation may be due to:

(a) Congenital variation in size and shape.
(b) Diseases of or injury to the pelvic bones or joints.
(c) Disease of the skeleton of the trunks or legs.

## Classification

Since the time of Deventer, who grouped pelves into types, too large, too small or too flat, there have been many attempts made to arrive at a complete classification of the anomalies, but from the nature of the case, none is wholly satisfactory. The classification familiar to all students can be found in any obstetrical text-book, but recent advances indicate a departure from this time-honoured listing. Caldwell and Moloy divide the female pelves into four major groups, according to their architectural characteristics. They call attention to the anterior and posterior segments of the inlet, with the widest transverse measurement as the dividing line; the variation in the sub-pubic angle; the anterior and posterior segments of the outlet and the size and shape of the sacro-sciatic notch. Based an these fundamentals, pelves are divided firstly into parent types:

(1) *Gynecoid or typically female type* inlet is round and typically female in all proportions.
(2) *Android or male type*—flat, male posterior segment; narrow anterior segment; forward sacrum and converging side-walls.
(3) *Anthropoid type*—long, oval inlet; antero-posterior diameter is long, transverse, narrow.
(4) *Platypelloid or Flat Type* — in which wide transverse and short antero-posterior diameters are salient characteristics.
(5) *Asymmetrical Pelves*—in which regular form is distorted.

Even the inexperienced observer will encounter little difficulty in recognizing examples of the parent types but the intermediate forms may. however, afford difficulty unless their anatomic relationship to the parent types and a general conception of factors which bring about the diversity of form observed in living women are clearly understood. Thus, the term "Android" is used to designate the female pelvis possessing a masculine type of posterior segment, although one should class it in a mixed type—an android with gynecoid tendency—in which the posterior segment shows typical male characteristics with fore-pelvis or anterior segment typically female or gynecoid.

A complete terminology for the individual pelvis must also include the lower pelvis. When a single term is used alone—for example—a gynecoid type—it is inferred that the lower pelvis is ample in all segments. When there occurs a significant departure from this ampleness in the lower pelvis such as a narrow sub-pubic angle, a forward sacrum or convergence of the side walls each feature is added separately in order to classify accurately the individual pelvis.

## Effects of Disproportion.

The value of this classification lies in that it attempts to clear up the maze

*Read before A.O.A., December 14th, 1936. —Abridged.

surrounding that large group of pelves to all intents and purposes clinically normal, yet which prove obstetrically to be the antithesis of normal. The android and anthropoid types, which to-day constitute, on the American continent at least, a large proportion of our female pelves are certainly partly responsible for the many unanticipated dystocias—poor engagement, occiput posterior, transverse arrest, etc. —experienced in everyone's practice. Malpresentations are four times more often seen in contracted pelves than in those of normal size and indeed transverse presentation is almost an indication that a deformity is present. With every centimetre of pelvic contraction the foetal mortality rises, except in the cases of absolute contraction where early recognition leads to elective Caesarean section and a consequent salvage of the babies. Asphyxia from prolonged pressure or cord prolapse; intracranial haemorrhage or pressure from fracture of the skull and fracture and dislocations of the long bones during traumatic delivery make up the account. The remedy lies as always in the early recognition of pelvic deformities and utilization of proper means to overcome their ill-effects.

## Recognition.

Before dealing with any question of an abnormality one must decide on a normal,—arbitrarily or otherwise. One is familiar with the anatomist's description of the female pelvis—made up of bones more delicate than that of the male, oval or cardiform shape of the inlet, wide sub-public angle,—but Dr. Thoms, completing a careful study of female pelves, concludes that the adult female pelvis is preferably round rather than oval, and Greenhill points out that judging from the large number of round pelves seen in X-ray pictures one would be inclined to believe that the oval or heart-shaped inlet may after some years not be considered the normal shape of the pelvis inlet. Recognition depends upon:

(1) Inspection of the woman.
(2) Pelvimetry—External and Internal.
(3) Roentgenological Examination.

Inspection amongst other things will note lameness, spinal curvature, peculiar gait and differences in the level of the two sides of the pelvis when patient is erect. Rachitic Rosary and square-shaped head will give information regarding rickets whilst a history of previous pregnancies, accidents to pelvis or debilitating disease especially during adolescence, are carefully noted. A markedly protuberant abdomen is frequently a sign of pelvic insufficiency.

With regard to external pelvimetry Dr. Thoms criticises the value of this procedure. Early in his work he learned that external pelvimetry fails to give uniformly accurate information as to size and shape of the superior strait. This is especially true in certain thin, undersized individuals in whom, although the external measurements suggested a generalized pelvic contraction, the roentgenograms disclosed a relatively capacious pelvis and spontaneous birth of the normal-sized infant was the rule. On the other hand, he noted that in many thick-boned, short, squatty individuals with similar external measurements, the roentgenograms revealed the presence of contracted pelves, and these patients presented during labour the problems usually associated with that entity. Shumann states that anyone who has taken routine external measurements over a considerable period of time should early recognize the unfortunate fact that the information obtained is of questionable value. De Lee and Greenhill have pointed out for years the unreliability of external measurements and many teachers are now doubting the wisdom of including them in their teaching-courses. They do give some general information as to the shape of the inlet and if they are markedly diminished may indicate some reduction in its size, but even this is not positive. They serve to indicate

the necessity for taking more careful internal measurements which are best and are receiving aid and reaching more dependable accuracy through the X-ray.

With regard to external pelvimetry of the pelvic outlet the situation is different. Here, the bony points to be measured are easily palpable externally and our measuration of the diameters should be reasonably accurate.

*Internal Pelvimetry*: For internal pelvimetry many devices have been invented, some of them most complex, some simple and ingenious but none of them wholly satisfactory. The procedure is too involved and too painful for practical purposes so that the method has been rather generally abandoned. No instrument can supplant the trained hand in estimating the form of the pelvic cavity and the obstetrician of experience can determine the availability of the pelvis from the standpoint of spontaneous delivery. The old gross error made by these men is their inability to reach a false promentory. Dr. Van Wyck has pointed out that the best pelvimeter is the baby's head and an estimation of the relative capacity of the pelvic inlet by using the foetal head as an index is a simple and fairly effective procedure. It is best done during the last two weeks of pregnancy and consists in locating the spine of the ischia with the vaginal finger (patient and examiner being aseptically prepared) and then having the patient exhale deeply, upon which the foetal head is grasped through the abdominal wall and firmly pushed into the pelvis, the vaginal hand determining whether it can be advanced to the level of the spines. This method is not available in very obese or unduly sensitive women but ordinarily is easy of performance and furnishes valuable information as to the outcome of labour in so far as the inlet is concerned.

**Roentgen Pelvimetry.**

The pros and cons of X-ray pelvimetry have been argued back and forth for many years. The method is still in a state of investigation and trial and one must not accept too literally the claims of its many ardent supporters. It is claimed to be the most nearly accurate method of determining the size and shape of the pelvis now at our command. From the groping efforts of Pinard and Tarnier in 1887 there has been an enormous advance to the precision and simplicity attained by modern technique. Hill's perimetric X-ray method of measuring the size of the foetal head and the pelvis deserves more than passing notice and one must also mention the stereoroentgenogram. It gives a startlingly beautiful three-dimentional picture of the foetus and the pelvis but optional defects may distort the picture and one's hands and wits must be used when interpreting the pictures. Taken all in all, X-ray pelvimetry is a step in the right direction towards clearing up the obvious defects of clinical pelvimetry.

Several methods of photographing and measuring the size of the pelvic inlet are in common use, the two most widely used being those developed by Johnston and Thoms. The latter's method is accurate to within 0.2 to 0.3 cms.—a negligible error.

Consultation with the Radiology Department elicits the information that Thoms' Centimetre Grid system is a relatively simple and inexpensive procedure. However, in obstetrical practice to get a complete X-ray outline of the pelvis, one should also have a stereo and a lateral plate, the latter giving necessary information regarding the sacro-sciatic notch, side walls of the pelvis and a comparative idea of the depth. Expense is, of course, a vital factor.

The importance of accurate pelvimetry in every primiparous woman should be kept in mind since the practice of successful obstetrics presumes a knowledge of all the facts that are essential for the successful outcome of labour and the important part played by the size and shape of the bony pelvis needs no emphasis. Even with a complete knowledge of the size and shape

of foetal head and bony canal, one does not have a complete picture of the course of the future labour since this is not similar to measuring a cannon-ball and the bore of a gun where passage only depends on accuracy of sizes. Many other factors come into play—moulding of the baby's head, polarity of lower uterine segment, giving of the symphysis—to mention only three.

### Treatment.

Once the diagnosis of contracted pelvis has been arrived at one must consider the course of treatment. For a successful outcome it would be wise to consider a case of dystocia a major surgical problem to be referred to a specialist's hands in an adequately equipped hospital wherever this is humanly possible. It should not be managed under unsatisfactory conditions or by untrained men, unless circumstances absolutely forbid the obtaining of more favourable conditions. We have several courses to consider, one or other being suitable for certain limits of availability of the pelvis:

1. Elective Caesarean Section.
2. Version.
3. Manual Rotation or Modified Scanzoni Manoeuvre.
4. Induction of Premature Labour.
5. A trial of labour.
6. Employment of various positions as aids, such as Walcher Position or Squatting Position where spontaneous delivery is attempted.

*Indications*: Conjugata Vera of 7.5 cms. or less constitutes absolute indication for Caesarean Section, since a living child of normal size cannot be delivered through such a pelvis. When discovered during pregnancy, the patient should be prepared for elective Caesarean Section shortly before term. Test of labour in such cases is of no value and only imperils the success of the inevitable section. If unhappily the condition is not known until the patient is well advanced in labour the treatment offers great difficulties. The child being still living and the mother in fairly good condition, the Low Cervical Section is the procedure of choice although there may be considerable risk of post-operative sepsis especially when many vaginal examinations and perhaps attempts at forceps delivery have been made. When the patient is definitely infected the Porro type of operation is the practical solution.

A true conjugate of 6 cms. or less is a definite contraindication for craniotomy since even the crushed skull and the body of the child cannot be extracted through such a canal. Under these circumstances therefore, the Caesarean Section must of necessity be invoked. It is unsafe to attempt a conservative hysterotomy in the presence of known infection. Obviously, if with the first child indication for a hysterotomy was a correctly diagnosed contracted pelvis the same conditions demand repeated section.

There are many types of Caesarean Section, of which three need be mentioned:

(1) The Classical (Sanger) Operation.
(2) The Low Cervical.
(3) Caesarean Section with hysterectomy—referred to as the Porro Operation.

Recent statistics show the low cervical operation to be much safer for the mother than the classical one, but here again the figures are open to criticism if it be remembered that the Laparo-Trachelotomy operation demands training and skill and is therefore done mainly by specialists whereas the classical one is used by the occasional operator and surgeon untrained in obstetrics. In potentially infected cases the low cervical operation is superior in that should infection occur its spread is more or less confined to the tissues under the bladder reflection of the peritoneum, and therefore tends to remain extraperitoneal and become a parametritis or pelvic cellulitis—a far safer form of sepsis than that involving the peritoneum generally This operation, popularized in America by

Beck and De Lee, should be performed before onset of labour if possible, the last two weeks of pregnancy being the most favourable time. It is far easier of performance when the patient has been in active labour for several hours since the stretching of lower uterine segment gives more room and draws the cervix away from the bladder. Besides its advantages in localizing infection, there is less likelihood of peritoneal adhesions, the scar in the uterus is stronger and hence rupture in subsequent pregnancies is minimized. A true test of labour is possible as uterine contractions rather aid the performance of the operation Moreover, some women who would otherwise have been subjected to section, may deliver by vaginal route after a test of labour.

Conjugata Vera of from 7.5 to 9 cms. constitutes relative pelvic contraction and here the treatment varies with the experience and skill of the obstetrician and facilities for adequate surgical procedure. If the patient be a multipara, the outcome of previous labours will prove a valuable guide, it being always remembered that multiparity presupposes children successively larger at birth, so that a woman who has undergone several traumatic forceps deliveries may present a totally obstructive labour because of the larger size of later babies. If the patient is in her own home and surgical skill and facilities are not available, she may be given a trial labour.

The term, *Test of Labour,* is applied to labours of varying duration and force of uterine contractions, the progress being carefully studied meanwhile in an attempt to evaluate the probable outcome. No generally accepted definition of a test of labour has been reached, some authorities depending upon the time element alone, others upon the frequency and force of the labour pains. Tweedy states a rule to the effect that as long as the mother's temperature and pulse-rate remain under 100, whilst foetal heart-rate remains over 100, neither is in danger and labour may be permitted to continue until some variation in one of the factors indicates impending disaster. During the progress of the Test of Labour all examinations are carried out with meticulous regard for asepsis, and no attempts are made at operative delivery. Upon the completion of the test period to the satisfaction of the obstetrician, the patient is either subjected to Caesarean Section if progress be unsatisfactory, or delivery is allowed to proceed to a spontaneous termination, forceps extraction or version being utilized if the normal outcome is too greatly delayed. The test of labour, whilst invaluable where conditions are adverse to Caesarean Section, has many inherent faults, since in the first place it is impossible to set up a standard. The utilization of the time factor or the severity of the uterine contractions is unsatisfactory since both elements vary so much in different women. Moreover, all too often, while one is observing a test of labour, the golden moment of election for hysterotomy is lost, the membranes rupture, or the woman becomes suddenly exhausted, is no longer a justifiable risk for section and labour must be terminated by some form of vaginal delivery with more or less disastrous consequences to mother and child.

Conjugata Vera of 9 - 19 cms. constitute the large group of minor contractions and are best managed by vaginal delivery, unless there is a strong element of foetal disproportion. In these women, malpresentations, posterior occiput, face presentations, etc., are common and must be diagnosed. Here a test of labour becomes the rule and the completion of engagement may be aided by employment of the Walcher Position. The latter is difficult to maintain, most uncomfortable to the patient and of little practical value. If labour is unduly delayed, forceps delivery is used, should transverse arrest occur, the Mann instrument is useful.

*Version* is an unsatisfactory procedure when any real disproportion is present. Either the membranes have long since ruptured and the uterus, be-

ing closely applied to the body of the child, renders the operation difficult and dangerous, or if it be resorted to early, the head has not been given time to mould and becomes an obstacle to easy delivery. When disproportion is but slight and the uterine contractions are not strong, then one may attempt version.

As previously mentioned, posterior positions and transverse arrests are very common in contracted pelves. *Manual Rotation* is the most effective method of securing anterior rotation of a persistent posterior occiput and should this fail, rotation by use of forceps may be attempted. This operation, called for years the *Scanzoni Manoeuvre*, was described by Smellie one hundred years before Scanzoni's account, so that the term is rather a misnomer. The original technique contemplates drawing the head down to the pelvic floor and there rotating it, whereas Bill and his followers believe that rotation should generally be done as soon as the cervix is dilated and effaced and while the head is still in the pelvic cavity. The truth probably lies between the two extremes and rotation should be done when it is apparent that labour is delayed and progress has ceased, be the head where it may, always provided the cervix is fully dilated and effaced. It is a dangerous procedure in the hands of careless or inexperienced men. Difficulty of securing true cephalic application leads to danger of injury to child, twisting blades rather than sweeping round in a wide circle,—as so ably described by De Lee in his Key Manoeuvre,—leads to extensive laceration of vagina by the tips of blades. With the usual type of forceps, subsequent to rotation the forceps are in an unnatural position for traction, requiring removal and re-application. Several instruments have been devised to overcome this difficulty and an excellent type has been invented by Dr. Mann of this school, who employs a split universal joint, permitting the forceps to finish in a normal position for traction to be applied.

*Induction of Labour* in cases of contracted pelves is almost universally used in England. It is based on the assumption that a premature child will be smaller, have a more malleable head and hence pass more readily through a contracted birth canal. Induction at the 34th or 36th week has been advanced as a solution to the problem but it is pointed out that the premature child has less chance of life than a mature one and the very softness of the skull makes the possibility of intracranial injury all the greater, so that, all in all, the infant mortality is increased by this practice, which as far as this continent is concerned, has been largely abandoned.

Absolute outlet contraction, where the sum of the bi-ischial diameter and posterior sagittal is under 15 cms. is an indication for elective Caesarean Section, since the probabilities of a living mature foetus being delivered through such a canal are very slight. If the condition is not discovered till late, section may still be performed if there is no infection. In cases of such, a Porro operation should be considered. Should this be impossible, forceps delivery may be effectual, although with a dead or injured baby a craniotomy may be necessary. The assumption of the squatting position which widens the outlet may offer some hope, but like the Walcher position, it is not usually of much avail.

One would like to dwell on some of the causal factors of contracted pelvis, but space forbids. Prophylaxis has been important in many districts. Until quite recently, due to the short period each year when the sun's rays are above the critical angle to the horizon plus improper feedings, Rickets was so common in Glasgow, Scotland, that deformed and contracted pelves were the expected thing and its treatment the main fort of the obstetrician. This preponderance is now largely absent through the improved education of the population to the use of Cod Liver Oil or Viosterol.

The pelvis of Osteomalacea, although rare in Canada, is prevalent in Italy, India and China. There is a

softening of bones which begins in pregnancy, although a first pregnancy, may go along normally and be unaffected. The pelvis is crushed in, completely deformed, and Caesarean Section is the only course left. This calamity can be diagnosed early but there generally is no pre-natal care—rather a long first stage and a doctor called too late. One can arrest the disease by means of the removal of the ovaries. Adrenalin is also believed to have some effect.

Even with a complete diagnosis of pelvic disproportion one cannot explain nor circumvent all dystocias. Many factors are unknown. A careful scrutiny of all dystocias over a period of several years in the Burnside Hospital, elicited the surprising facts that pelvic disproportion was present in a surprisingly small percentage of cases, that a much greater percentage showed normal external measurements, yet dystocias appeared, and that many expected dystocias turned out amazingly easy labours.

All obstetricians have met the broad-shouldered flat-chested, muscular type of female—masculine in build—who has difficult labours. Is there an endocrine factor?

Also there is the labour in which, although everything about it is completely normal, the cervix for some unknown reason refuses to dilate and efface with labour apparently interminable. Is there some factor "X," whose presence conditions such eventualities as an easy first pregnancy with a very difficult second or vice versa, some inherent factor of the uterus about which we can only make conjectures?

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**ERRATA.**

In the December issue of this Journal, page 39, Dr. Morris Fishbein was mentioned as author of "One Hundred Million Guinea Pigs."

To A. Kallet and F. J. Schlink, the correct authors, we express our regrets.

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# THE DIAGNOSIS AND INDICATIONS FOR TREATMENT OF BILIARY DISEASE ASSOCIATED WITH JAUNDICE.

By J. P. FLETCHER, M.A., '37.

## Introduction.

Jaundice is the condition in which the tissues and secretions of the body, except the central nervous system and cerebro-spinal fluid, are stained yellow colour, due to hyperbilirubinaemia. Such may occur under the following conditions:

A—INADEQUATE EXCRETION OF BILIRUBIN BY LIVER.

*Toxic or Infective Jaundice,* in which toxaemia, poisons, spirochaetes, and unknown agents injure liver cells, so that

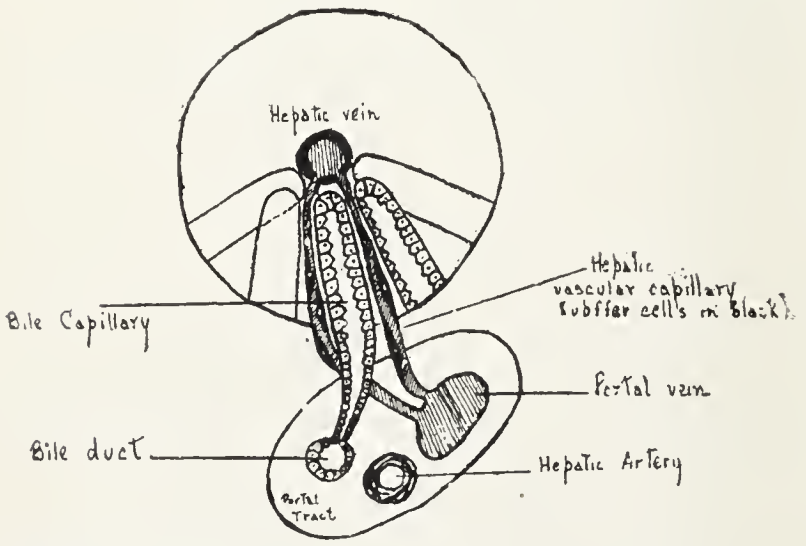


Diagram of Structure of Liver Lobule - McNee.

inadequate excretion occurs. Also, when liver cells are severely damaged, some of the bile canaliculi rupture, allowing some of the excreted bile to reach the liver capillaries and to be re-absorbed. This is readily appreciated if one believes McNee's diagram of the structure of the liver lobule to be correct.

Consequently, although the hyperbilirubinaemia may at first be due to accumulation of bilirubin bound to protein (unexcreted by liver cells and giving indirect Van den Bergh reaction), secondarily free bilirubin (excreted by liver and giving direct Van den Bergh reaction) circulates in the blood.

B—OBSTRUCTION TO BILIARY DRAINAGE.

*Obstructive Jaundice,* in which disease of biliary tract causes damming back of bile, so that the bile canaliculi rupture, allowing free bilirubin to circulate in the blod, which gives a direct Van den Bergh reaction. However, since infecton is prone to develop in obstruction, hepatitis often occurs, so that combined bilirubin circulates, also. Consequently the Van den Bergh test may fail to distinguish jaundice of types A and B.

C—EXCESSIVE PRODUCTION OF BILIRUBIN.

*Haemolytic Jaundice,* in which the red blod cells are destroyed abnormally rapidly. This occurs typically in icterus neonatorum and haemolytic icterus, in which liver and biliary tract are thought to be normal, although Rich believes that liver function must be depressed. It also occurs in severe toxaemias (e.g., pneumonia) and haemolytic poisoning, although in these cases mechanisms A and B are also involved.

It is with the obstructive type that we shall deal primarily in this paper, although it will be appreciated that differential diagnosis will demand consideration of the other types.

## Biochemistry and Pathological Chemistry of Obstructive Jaundice.

(a) *The Bile.*

The biliary tract consist of a system of ducts which store, concentrate, and discharge bile into the intestine at the proper time to fulfil its functions of essential emulsification of fats and activation of pancreatic lipase. By means of its bile salts, it destroys most bacteria which it meets and acts as a vehicle for the excretion of cholesterol and lecithin, which are water-insoluble,

and for the absorption of fatty acids in the gut. Andrews et al believe that in an inflamed gall-bladder, bile salts are absorbed, thereby allowing cholesterol to be deposited, forming stones around any nidus.

Cholesterol is excreted by the liver and is the main constituent of all gall-stones, except the pure pigment stones found in haemolytic jaundice. In addition to decrease in bile salt concentration of bile, hypercholesterinaemia, stasis of bile, and infection of the biliary tract are important factors in the formation of gall stones.

Bilirubin is an iron-free, protein-free, yellow pigment formed from haemoglobin in the reticulo-endothelial cells in bone marrow, liver and spleen, essentially. It may also beliberated in appreciable quantities from large haematomas. It is excreted by liver into bile canaliculi. It is thought to be transported in serum ordinarily combined with protein, which can be excreted by the kidney only when a 1—12,000 is reached, whereas, bilirubin freed of protein by liver cells can be excreted by kidney at a threshold of 1—50,000.

(b) *Certain Laboratory Tests Useful.*

(i) Urinanalysis — for bile and urobilin — repeated daily is of great value.

(ii.) Observation of stool—colour tells if bile pigment present; if bulky and offensive in odour, means that pancreatice duct is blocked.

(iii.) Van den Bergh test — qualitative test has already been discussed; quantitative test is of no greater value than icterus index.

(iv.) Icterus index—is a much simpler test than the above; it measures hyperbilirubinaemia accurately.

(v.) Duodenal tube aspiration — by means of which one may analyze bile and determine whether pancreatice juice reaches the duodenum.

(vi.) Galactose tolerance test—in which one determines the ability of liver to synthesize glycogen from galactose. 40 grams galactose are fed. If more than 4 grams appear in a 5-hour sample of previously sugar-free urine, damage to liver has occurred.

(vii.) Serum phosphatase — phosphatase is excreted chiefly in bile, therefore, in obstructive jaundice, quite high values occur in blood; whereas, in uncomplicated other forms, normal or slightly raised values occur.

(viii.) Cholecystography — is now much used and, if positive, quite significant. 5-7 grams of tetraiodophenolphthalein is given by mouth after the evening meal. Fourteen hours later, X-ray of gall bladder region is taken. Then fat, usually egg yolks and cream, is fed and X-ray taken in four or five hours. Normally, the first plate should show a uniform shadow of the gall bladder; whereas, the second should not show it. Stones in gall bladder usually show as a defect in the shadow. If the gall bladder shadow does not disappear, it is called "malfunctioning," and is significant of disease. If no shadow appears, the dye may not have been absorbed by gall bladder mucosa, or may be unable to enter the gall bladder. Failure of absorption by the gut may be checked by intravenous injection. If normal function is recorded, one may still over-rule this evidence if the clinical evidence is strong.

(ix.) Cholangiography — Injection of radio-opaque liquids into the common bile duct via a T-tube is employed to determine, the patency of fine biliary radicles and ampulla of Vater and regurgitation into pancreatic duct.

## Etiological Classification of Obstructive Jaundice, With Notes on the Pathology.

A—CONGENITAL.

*Atresia of Bile Ducts.*—Uncommon; fibrosis of ducts may occur in portal region with ducts below being patent, i.e., biliary cirrhosis; the gall bladder will be filled with mucus.

B—ACQUIRED.

1. *Trauma.* — Stricture of ducts or stenosis of ampulla of Vater due to ulceration by gall-stone or occasionally, injury by a surgeon. Dilatation occurs above it.

2. *Inflammation.* — Infection of the biliary tract either the primary factor in a sequence leading to obstruction and complications or, secondarily, in obstruc-

tion. The portal blood is normally infected with bacteria and the lymphatics from liver, gall-bladder, and pancras have been shown by Graham to anastomose, so that infection spreads easily. Against this, the defence of bile, which destroys most bacteria, is fairly adequate. But if interference to blood supply or obstruction to the passage of bile occurs, infection is very likely.

Chronic infection differs from the usual gamut, in that tuberculosis and syphilis are rare.

(a) *Catarrhal Jaundice.* — The pathology is poorly understood, but it seems likely that the function of liver cells is depressed and that oedema of bile canaliculi and ducts occurs. Bile is viscid and contains desquamated epithelium with few pus cells.

(b) *Cholangitis* results from cholecystitis, cholelithiasis, hepatitis, and severe systemic infection.

(i.) Acute Suppurative. — There is great dilatation and thickening of the ducts with pus and bile in the lumen. Pericholangitis, fistulae, peritonitis (bile), and abscesses of liver are liable to occur.

(ii.) Acute Non-suppurative.—Occurs in catarrhal jaundice.

(iii.) Chronic.—Results in precipitation of cholesterol and pigment-forming "mud." Cholelithiasis is usually present. Infective biliary cirrhosis is liable to result.

3. *Neoplasm of Bile Ducts.*

(a) *Benign.*—These are rare and are usually papillomas.

(b) *Malignant.* — These are carcinomata, almost always.

(i.) Primary. — Uncommon; rare; occur most often at at ampulla of Vater or at junction cystic hepatic and common ducts. These tumors are small, white, firm, feel-like stone within the duct or at the ampulla.

(ii.) Secondary. — Are probably more common and follow carcinoma of gall bladder, head of pancreas, and liver.

4. *Metabolic.* — Gall stones will be considered under this caption for convenience. Stones impacted in the cystic or common duct or in ampulla of Vater are almost always formed in the gall bladder. Obstruction is usually not complete, but onset of cholangitis will make it so. Pancreatitis is likely to occur if obstruction at the ampulla involves the pancreatic duct.

5. *Nervous Control Malfunction.* — Biliary dyssynergia or dykinesia.

This is probably very common, but probably uncommonly causes jaundice directly. Spasm of the sphincter of Odi, with or without contractions of gall bladder, may reproduce biliary colic pain and may be responsible for the onset of pancreatitis if biliary infection is present. This causes also the condition called, by Westphal and others, the "static gall bladder," which is very prone to contain stones and is hypertrophic or else atrophic.

## Diagnosis, Differential Diagnosis, and Indications for Treatment.

Jaundiced patients are usually quite sick, but rarely require emergent surgical intervention. Consequently, one has a day or more to establish the diagnosis, which is often very difficult.

### A—CONGENITAL ATRESIA OF BILE DUCTS.

Beginning at birth or shortly afterwards, jaundice sets in and progresses steadily. The stools are greyish-white in colour and the urine brown. Haemorrhage occurs from skin, mucous membranes, and umbilical cord. Loss of weight occurs. Death results in a few weeks. Treatment is of no avail.

Differential diagnosis concerns prolonged icterus neonatorum, haemolytic icterus, and pylephebitis from umbilical cord infection.

(i.) Icterus neonatorum—the stools are normal in colour constantly, although the urine may contain bile; blood clotting time is normal. (ii.) Haemolytic icterus—a family history,

lack of bile in urine, and increased fragility of red blood cells establish the diagnosis. (iii.) Pylephlebitis—septic fever with haemorrhages from umbilicus or mucous membranes occurs at about the fifth day after birth.

### B—ACQUIRED OBSTRUCTIVE JAUNDICE.

For convenience, the causes will be discussed in an order which is frequently a sequence of events.

1. *Metabolic—Cholelithiasis.*

A patient, usually over 40 years of age, is suddenly seized with an attack of paroxysms of severe lancinating pain in the upper right quadrant of the abdomen or in the right epigastrium and radiating to the right side of back or shoulder, with nausea, vomiting, and severe sweating. History is of daily indigestion for years, characterized by belching of gas, and made worse by certain foods, especially fat, fried foods, and pastry. Examination reveals tenderness over gall bladder, slight leucocytosis and perhaps slight fever will be noted. Mild icterus and bilinuria may be noted the following day. The attack lasts only a few hours and if morphia is given, he is free of pain, until its effect wears off. These attacks tend to occur at intervals of months or years. Infection is very liable to occur in gall bladder, cystic or common bile ducts, causing more marked icterus, clay-coloured stools and bilinuria to appear and remain for a day or so. Also, fever and chills will now be a definite feature of the attacks. Loss of weight is fairly marked. An area of hyperaesthesia may be noted to the right of ninth to twelfth thoracic vertebrae and is reliable as a sign of biliary tract disease. Even without the presence of jaundice, one might be certain that such a patient suffered from cholelithiasis with mild cholecystitis and/or cholangitis. Surgical removal of gall bladder and stones from common duct is indicated, but must be delayed until jaundice and fever have nearly subsided, or else, if this does not occur in a few days, fluids, glucose, calcium chloride and repeated blood transfusion precede operation. Cholecystectomy is done (unless acute inflammation is present), the common bile duct is opened, searched for stone, stricture, and stenosis of ampulla of Vater. If fever or obstruction have been present, a T-tube is left in the common duct; otherwise, it is repaired. A drainage tube is always left in Morrison's pouch (peritoneal cavity). If in such a patient there had been no history of jaundice, the surgeon would not likely open and explore the common bile duct unless a stone could be felt, the duct is thickened or dilated (indicating obstruction) or the head of pancreas is hardened Post-operatively, in severe jaundice, blood transfusions, glucose, calcium salts and fluids are necessary. Before removal of the T-tube, jaundice and fever should be gone, the bile should be clear and free from precipitate and one should be able to inject sterile saline into the T-tube without difficulty. If more exact knowledge of pathology, such as spasm of ampulla of Vater, fistulae or pancreatitis are desired, cholangeography may be employed.

However, diagnosis is not always easy, for colic may never occur, jaundice may be unnoticed by the patient, vague epigastric discomfort and loss of weight being the only symptoms. On the other hand, jaundice may be marked, but secondary hepatitis may make it indistinguishable from the toxic type. It is of exceeding importance that a stone in the common bile duct causing jaundice be treated surgically. The differential diagnosis concerns catarrhal jaundice, pancreatitis and carcinoma, obstructing common duct or ampulla of Vater especially.

(i) Catarrhal jaundice may prove very confusing for a super-added complete obstruction to the biliary radicles is often present, so that clay-coloured stools, presence of free bilirubin (in addition to combined) in the blood and biliuria without urobilinuria occurs. The galactose tolerance test, indicating reduced liver function, is the only test

that will decide the problem, and if hepatitis, secondary to obstruction by stone, is present, this is of no use. However, most often in a day or so in catarrhal jaundice, pigment will return to the stool and urobilin appear in urine in large quantities.

(ii.) Pancreatitis usually occurs in a patient who has had biliary disease. In acute cases, the excruciating pain and extreme tenderness over the pancreas differentiate; in chronic cases, the findings will be very similar, except that the stools will be large, fatty and foul. Trypsin-free duodenal contents favours the diagnosis, but does not eliminate the possibility of stone in the ampulla of Vater. Glycosuria favours the presence of pancreatitis.

(iii.) Carcinoma obstructing the duct may give the picture of chronic pancreatitis or biliary colic, with intermittent jaundice, if infection supervenes. Presence of pain one to two hours after meals favours the diagnosis of carcinoma. However, typically, obstruction to the common bile duct, due to tumour, results in an insidious onset of progressive jaundice, often without pain, the presence of a large pear-shaped gall bladder favours the diagnosis (Courvoisier's law).

Moynihan, Wilkie, Martin and others strongly advise that, if reasonable suspicion exists that stone in the common bile duct is causing obstruction or toxic jaundice, laparotomy should be done, for obstruction will cause severe damage to liver (hepatitis, biliary cirrhosis) and pancreas. Martin claims that not much harm is done if a patient with catarrhal jaundice is explored.

2. *Inflammation.*

(a) *Catarrhal Jaundice.*

This disease tends to occur in children and young adults and is characterized by upper respiratory infection, followed in some day by malaise, anorexia and slight jaundice. Mild fever and mild pain in right upper quadrant of abdomen may occur. Jaundice progresses so that stools may become clay-coloured and biliuria occurs. On examination, liver, gall bladder or spleen may be palpable. There are no indications for surgical intervention, for all recover on rest in bed with high carbohydrate diet with fluids. Differential diagnosis concerns Weil's disease, toxic hepatitis, obstruction of common bile duct by stone, and mild cholangitis. (i.) Weil's disease has sudden onset with high fever and deep jaundice. (ii.) Toxic hepatitis may stimulate it for a week or so, but history and onset of severe symptoms differentiate. (iii.) Mild cholangitis gives much the same picture as obstruction of common duct, to which it is often secondary. Since hepatitis is very often present, diagnosis likely depends upon the fact that the patient is an older adult, who has suffered attacks of biliary colic or cholecystitis. Also, jaundice may fail to clear up on treatment for catarrhal jaundice.

(b) *Cholangitis.*

(i.) Acute Suppurative.—A patient who has suffered from biliary colic, cholecystitis or severe infection may suddenly be seized with severe chills, septic fever and jaundice. Examination reveals enlargement and tenderness of liver, and definite leucocytosis. This disease and acute gangrenous cholecystitis are the only true emergencies in biliary surgery. Intravenous fluids, glucose, calcium salts and blood are essential pre- and post-operatively. At operation, evacuation of pus and bile and insertion of T-tube and drainage tubes must be done. Pericholangitis, fistulae and bile peritonitis may complicate this disease. The latter is highly fatal. Differential diagnosis involves suppurative pylephlebitis and liver abscess, both highly fatal, which closely resemble this condition. A history of appendicitis will usually serve to differentiate them, but even if the common bile duct were exposed and drained, no harm would be done.

(ii.) Chronic. — A patient who has had acute cholecystitis or biliary colic may develop recurring attacks of chills, fever, sweating and pain similar to mild

biliary colic. Jaundice, clay-coloured stools and dark urine are noted the following day, but pass off in a few days. Operation need not be done at once, but when the fever is down, drainage of common bile duct by T-tube and removal of gall bladder or stone in common duct or dilatation of a tight ampulla of Vater is done. Pre- and post-operative treatment is the same, but need not be so intensive as in the acute suppurative form.

(c) *Cholecystitis.*

(i.) Acute.—This disease is discussed in detail in another paper in this issue. A patient who has suffered from biliary colic may suddenly develop severe pain in the right upper quadrant of the abdomen, with fever, nausea and vomiting. Examination reveals great tenderness and muscle spasm and a mass in the right upper quadrant. Jaundice occurs frequently. Leucocytosis is moderate. Treatment is expectant unless gangrene impends, when cholecystostomy is done. Cholecystectomy is done when the acute inflammation is gone. Cholangitis and hepatitis and peritonitis are serious complications.

(ii.) Chronic. — The symptoms and history are often inseparable from those of cholelithiasis, which is most often present. Jaundice is not so frequent as in the latter condition. The use of duodenal tube resulting in failure of B bile (concentrated in gall bladder) to appear repeatedly when bile is obtained suggests this disease. Presence of leucocytes, epitehlial cells, and excessive mucus indicate inflammation in the biliary tract, whereas cholesterol and calcium bilirubin crystals suggest cholelithiasis. The cholecystogram may be used to confirm the diagnosis. Treatment by cholecystectomy does not produce such high percentage of cures if disease is mild, but Wilkie, Phillips and others state emphatically that the complications — cholelithiasis, cholangitis, hepatitis, and possibly toxic effects on joints, heart and kidneys are mighty reasons why early removal should be done. Wilkie states that if the general health is improved, the percentage of cures is very high. Differential diagnosis concerns cholelithiasis, cholangitis, and mucous colitis and duodenal ulcer in the female.

3. *Neoplasm of Bile Ducts.*

An older adult who complains of onset of digestive disturbances, followed by slow progressive jaundice, with or without pain in epigastrium or right upper quadrant, one must suspect carcinoma of gall bladder, pancreas, ampulla of Vater or bile ducts. Loss of weight is often no more marked than in obstruction, due to stone. Treatment is merely palliative and cholecystgastomy or duodenostomy will relieve itching mental depression, headache, yellow vision, and terminal delerium, due to bile in the blood and tissues. Differential diagnosis is important. for obstruction, due to stone, may simulate malignant obstruction. If infection is superadded, cholangitis and pancreatitis must be considered.

4. *Trauma.* — Stricture of common bile duct or stenosis of ampulla of Vater.

A patient who develops attacks of mild biliary colic one to two hours after meals with a gradual onset of jaundice, may have either stricture or stenosis, if he has a history of biliary colic or operative interference with the biliary tract. Treatment is surgical cutting of stricture or stenosis. Differential diagnosis concerns malignant obstruction.

5. *Biliary Dyssynergia.*

Best and Hick believe that it is not uncommon for a patient, who has had cholecystectomy, to suffer mild or moderate attacks of biliary colic, with with or without jaundice. Heretofore, these patients have probably been considered as suffering from anxiety neurosis, except when jaundice occurs. They have shown by cholangiography that spasm of the sphincter of Odi may persist for hours or even days, but it is likely that aedema has occurred in prolonged attacks.

Morphine has been shown to increase pain until the drug acts centrally, whereas glyceryl trinitrite or amyl nitrate relieve spasm and pain.

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# DIAGNOSIS AND MANAGEMENT OF ACUTE CHOLECYSTITIS.

By R. A. GORDON, B.Sc., '37.

This paper will deal, as the title suggests, only with the problems of diagnosis and management of acute cholecystitis, and no attempt will be made to enter into a discussion of the aetiology and pathology of the condition.

The problem of diagnosis of acute cholecystitis is the problem of differential diagnosis of acute conditions within the abdomen. The problem of management of the disease once the diagnosis is made is one of statistics, and hinges around the question of whether at that point it is more necessary to treat the patient or the local lesion from which he suffers.

Acute cholecystitis in nearly all cases occurs in patients who have a previous history of cholecystic indigestion, and frequently of previous attacks of abdominal pain suggestive of biliary colic. The onset may be sudden, with pain starting in the right hypochondrium or in the umbilical region and gradually settling in the right hypochondrium, which is tender and does not move on respiration. There is often pain in the back in the subscapular region, and vomiting may be present. Belching and shivering frequently occur. A tender rounded mass can be detected on palpation projecting beneath the costal margin and moving downwards on respiration. This mass may reach to below the umbilicus, and is tender to the touch. If the swelling is gall-bladder it is dull on percussion and has no resonance between it and the costal margin.

Acute cholecystitis must be differentiated from acute disease in the chest (pleuritis), coronary thrombosis, acute conditions of the right kidney, perforated duodenal ulcer, acute appendicitis, acute pancreatitis (which is frequently associated with it) and acute cholangitis. Pleurisy will usually be readily differentiated by the findings in the chest. The pain distribution in coronary thrombosis should assist in the differentiation in that case, and there will be no point of tenderness in the right upper quadrant. Pancreatitis can rarely be diagnosed with accuracy, and is almost invariably associated with a diseased gall-bladder. The cases in which it is important to make an immediate differentiation are those in which surgical intervention is urgent, viz., perforated duodenal ulcer, acute appendicitis, and acute cholangitis. It should be remembered that in none of these cases will there be a palpable tender gall bladder. In the differentiation between perforated ulcer and acute cholecystitis, where difficulty arises, examination of the patient under the fluoroscope may assist in clarifying the diagnosis by demonstrating the presence of a gas bubble under the dome of the diaphram, a finding which suggests that the patient is suffering from a perforation, although its absence does not eliminate that possibility. If difficulty arises in differentiating between a case of acute appendicitis and an acute cholecytitis, the abdomen should probably be opened through a gridiron incision and the appendix examined.

It is imperative to differentiate between acute cholecystitis and acute cholangitis, since the latter condition requires urgent drainage of the biliary system. Jaundice is a frequent accompaniment of acute cholecystitis due to extension of the oedema to the bile duct from the inflamed Pouch of Hartman of the gall-bladder. In such a case the gall-bladder will be enlarged and palpable. The presence of obstructive jaundice with fever and no palpable enlarged gall-bladder suggests cholangitis, and when this diagnosis is

made the necessity for early drainage of the biliary tract by a simple type of operative procedure is urgent.

With reference to the differentiation between acute conditions in the right kidney and acute cholecystitis we may consider the history and findings in the case of a patient where the diagnosis of acute cholecystitis was made, and where subsequent investigation showed conclusively that the symptoms were due to a lesion not in the gall-bladder, but in the right kidney.

This patient, Mrs. Q., was perfectly well until one week before admission to hospital. At that time she experienced a slight chill which was followed by severe pain in the right upper quadrant of the abdomen, and by vomiting. The pain radiated to the right side of the back, to the right flank, across the abdomen, and down the right thigh and leg to the foot. The pain had persisted, as had the vomiting. She had passed a great deal of flatus, and the abdomen had become greatly distended. She had suffered from an attack of a similar nature ten years before, which did not last long. There had been no jaundice or specific food intolerance, but there had been some post-prandial belching of gas for several years. There had been increased urinary frequency during the year prior to admission, but there had never been burning or pain, and the patient had never noted blood in the urine. On admission the abdomen was markedly distended and tympanitic. There was tenderness on the right side extending from just below the costal margin to about the level of the right iliac crest. There was no marked tenderness in the costovertebral angle. A mass was palpable in the abdomen extending from just below the costal margin anteriorly to about the level of the iliac crest and forward to just inside the mid-clavicular line. This mass was tender, rather uneven on palpation, and felt more prominent in the flank than in front, while percussion and palpation revealed the presence of bowel containing gas over its anterior surface. The edge of the liver was palpable above the mass and just below the costal margin.

This history was immediately suggestive of an attack of acute cholecystitis. The attack ten years previously and the story of indigestion and the belching of gas were easily interpreted as a rather typical story of cholecystic indigestion and biliary colic in a woman fifty years of age who had had eighteen pregnancies. The patient was a swarthy Italian woman, and in the artificial light in which she was first seen it was difficult to eliminate the presence of a slight degree of jaundice. Acute cholecystitis in nearly all cases occurs in patients who have had a previous history of cholecystic indigestion and, frequently, of biliary colic.

The history of this patient, therefore, was more suggestive of acute cholecystitis than of any other condition, while there were practically no urinary symptoms to point to the possibility of a lesion in the kidney. Certain of the physical findings, however, made one suspect that the offending organ was the kidney, rather than the gall-bladder. The radiation of the pain to the lower extremity on the same side was not readily explicable on the diagnosis of acute cholecystitis, although it was suggested that this might occur in case of a perforated gall-bladder with an abscess lying against the posterior abdominal wall. Moreover, this mass was more prominent in the flank than anteriorly, as one would expect of a tumor arising in the kidney, and there was bowel anterior to the mass, a finding which would be very improbable in the case of gall-bladder tumor. The presence of great quantities of pus in the urine was definitely suggestive of a kidney lesion, although that might conceivably have been due to the presence of an acute inflammatory mass in the region of the ureter. N.P.N. was 140.

X-ray examination showed that this patient has stones in both her ureters, and that both kidneys were enlarged, the right one, however, being the larger. Nephrostomy on the

right side was rewarded by the drainage from the kidney pelvis of about 100 ounces of pus.

On admission this patient had been vomiting for a week. She was obviously very ill and dehydrated, and was suffering considerable pain both from the acute inflammatory condition in the kidney, and from her abdominal distension. The diagnosis was not certain, but there was obviously, in this case, no urgent need for any surgical procedure. The patient had been ill for a week, and there had been no recent development which would indicate the necessity for immediate surgical intervention. The patient was extremely ill, and in no fit state to withstand the strain of an intra-abdominal operation. Her serious condition was not due to the acute lesion in the abdomen, or outside of it, whichever it might ultimately be shown to be, but due to a secondary biochemical upset incident to her dehydrated condition, and nervous fatigue and shock resulting from the long weeks of pain. The rational procedure was to correct these secondary metabolic disorders in as far as possible, and to give the patient rest before making any attempt to correct the primary condition. If this was to be done, there was obviously no necessity for an immediate and certain diagnosis of the condition. The fluid and sodium chloride which the patient had lost from her tissues during the week of dehydration were replaced by the administration of physiological salt solution intravenously. Nourishment was provided by the addition of 5% glucose to the saline, an addition which would have the additional value of protecting the liver parenchyma from degenerative influences had the lesion been in the biliary tract. In addition the patient was given relief from pain, and by this means rest, by the administration of codeia and the application of heat in the form of an electric cradle over the abdomen. Under this treatment her condition rapidly improved to the point where surgical measures for the relief of the primary condition might be deemed safe. Had this patient been suffering from acute cholecystitis the rationale and plan of treatment would have been identical.

Little more need be said about the diagnosis of acute cholecystitis. It should be added, however, that all those writing on the subject are agreed that there is no parallelism between the severity of the clinical symptoms and the severity of the pathological lesion in the gall bladder.

Such unanimity on any phase of this subject is rather surprising when one scans the great amount of controversial and contradictory matter written and reported concerning the merits of various methods of therapy. Roughly one may place all those who concern themselves with the subject in one of two classes, namely:

1. Those who draw a parallel between acute appendicitis and acute cholecystitis and advocate immediate removal of the organ when the diagnosis is made.

2. Those who believe that the gall-bladder should be removed following an attack of acute cholecystitis, but that the operation should be delayed for a greater or lesser interval of time until the patient can be adequately prepared for operation by the administration of intravenous saline and glucose and the alleviation of shock. Some writers in this latter group advocate removal of the organ at the earliest possible moment, while others prefer to wait until the inflammatory process has subsided sufficiently so that the patient's temperature becomes and remains normal.

Those who advocate immediate operation when the diagnosis of acute cholecystitis is made tend to emphasize the importance of forestalling gangrene and perforation of the gall-bladder, and draw an analogy between this condition and acute appendicitis. Study of the question reveals, however, that the frequency of perforation of the gall-bladder and peritonitis is very small. Certainly it is not as great as the proponents of immediate operation

for this condition would lead us to believe when they draw an analogy between this condition and acute appendicitis. H. F. Graham reports the operative results in one hundred and ninety-eight consecutive cases of acute cholecystitis, with ruptured gall-bladder in seven cases where operation was delayed, and with local peritonitis in two, but no case of general peritonitis. In five hundred and eight cases reported by Judd from the Mayo clinic, 3, or 0.59%, had a general peritonitis. In a series of cases reported by Dr. R. R. Graham from the Toronto General Hospital, 1.47 per cent. had general peritonitis.

Judd and Parker, reporting 1,115 operations on the gall-bladder and bile ducts at the Mayo clinic (of which 854 were cases of cholecystectomy) observe that in patients dead post-operatively the deaths could not usually be attributed directly to the actual operative procedure or to conditions in the biliary tract. On such observation is based the "delayed" treatment of patients with acute cholecystitis. Actually the delay in treatment refers only to surgical procedures. The patient with an acutely inflamed gall-bladder comes to the surgeon usually with a disease far more serious than the local lesion in his gall-bladder. This disease is a general metabolic and biochemical upset of the whole organism, and is far more dangerous to life than any acute inflammatory process in the body. The poor results obtained in the "delayed" treatment of acute cholecystitis have been due to the fact that the process was actually a failure to treat the patient while the local lesion commanded the center of the stage, and by progressing demanded operation, or recovered spontaneously. During this period of "delay" what happened to the patient? The serious metabolic disturbance which he had been suffering became progressively worse, so that when operation was undertaken the risk was greatly increased by the poor condition of the subject. The mortality was naturally greater than if operation had been undertaken when the patient was first seen.

The most satisfactory result in these cases will be obtained by treating the patient before undertaking the correction of the local lesion. By this, one means that firstly the serious state of dehydration, disturbed metabolism and starvation must be relieved. The patient must be given rest by the alleviation of pain. Meanwhile the local lesion should be observed for signs of progression. In most cases the patient's general condition will rapidly improve with such treatment, and with rest the acute disease in the gall-bladder will subside. Operation on the gall-bladder may then be undertaken in comparative safety. Further argument for this procedure is found in the surprisingly frequent association of diabetes and cardiac disease with this condition of the gall-bladder,—factors which absolutely contra-indicate operation under any but the optimal conditions of safety if it is at all possible to obtain these.

On the surgical services of the Toronto General Hospital an attempt is made to defer operation in treating cases of acute cholecystitis. Sleep is assured by the application of heat to the abdomen and the administration of sedatives. Dehydration and starvation are combatted by the administration of glucose in saline intravenously, giving about 3,000 c.c. of 5% glucose in saline in 24 hours. Unless the pain persists without diminution and unless the condition of the patient becomes progressively worse operation is delayed until the temperature has been normal for some time, when an elective operation may be performed. This period of deferment also gives an opportunity to treat any associated disease process, such as diabetes and cardio-vascular disease, and to assess the fitness of the patient for operation. Should the patient fail to progress or become worse, operation must be undertaken.

In the final analysis, the merits of any method of therapy must be assessed on the results obtained. In a series of

cases operated upon at the Toronto General Hospital, and reported by Dr. R. R. Graham, the total operative mortality was 5.8 per cent. The mortality in those cases where operation was delayed in accord with the above plan was 4.8 per cent. The mortality in this group compares favourably indeed with the mortality reported by those surgeons who advocate and practice immediate removal of the gall-bladder for this disease. H. F. Graham reports a mortality of 5 per cent. in a small group of 20 cases, in which the procedure was immediate operation, and compares this with a mortality of 6.2 per cent. in a group in which the operation was delayed for 48 hours or more. Pratt reports a mortality of 22.2 per cent. in a series of 45 cases, in which 40 were subjected to immediate operation, while five others were prepared before operation. Taylor, advocating pre-operative administration of glucose solution, but operating while the acute cholecystitis is still active in most cases, reports a mortality of 16.3 per cent. in a series of 129 cases of acute gall-bladder disease. Bass and Bird report decreased mortality by the pre-operative administration of fluids, glucose and rest.

The type of operation to be performed must receive some consideration. Generally, mortality is much higher where the operation is cholecystostomy than where cholecystectomy was done. Fowler, in an analysis of the end-results of therapy in 1,000 cases of gall-bladder disease, reports a mortality of 12.8 per cent. in cases of acute cholesystitis, where cholecystostomy was performed, as compared with a mortality of 6.5 per cent. in those cases where cholecystectomy was done. It seems to be agreed that cholecystectomy is the operation of choice.

It has been stated that if these patients were operated upon during the first 48 hours after the appearance of symptoms that there would be no mortality. Unfortunately, however, the surgeon rarely sees these patients in this period. It should be remembered, too, that should operation be possible at this time, it will not prevent a tragedy, should there be stones remaining in the common duct.

## Summary.

1. Acute cholecystitis occurs in nearly all cases in patients who have a previous history of biliary tract disease and must be differentiated from pleuritis, coronary thrombosis, acute conditions in the right kidney, perforated duodenal ulcer, acute appendicitis, acute cholangitis.

2. Acute cholecystitis is considered by some to be analogous to acute appendicitis and to require immediate operation. Better results in the treatment of the condition appear to be obtained by treating the patient's general metabolic and biochemical upset and allowing the acute process in the gall-bladder to subside before operation is undertaken. Associated disease processes should be treated during this period of deferment.

3. Immediate operation is indicated if the patient's condition fails to improve under conservative treatment, or if it progresses.

4. Cholecystectomy is the operation of choice in the treatment of the disease.

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# TREATMENT OF EPILEPSY

By ANNE KEYL, B.Sc., '37

Any patient coming to his physician complaining of recurring fits is entitled to a thorough investigation, to ascertain whether the condition be organic, functional or idiopathic in origin. If the diagnosis be epilepsy, every effort should be made to discover whether there is an organic basis for it. This investigation entails a thorough physical, including a neurological, examination, examination of spinal fluid, and, if necessary, an encephalogram. If an organic defect be found in the nervous system, surgical interference may be advisable. If the condition be idiopathic, medical treatment as outlined below is instituted.

Other physical defects, such as foci of infection, eye defects, etc., should be corrected as soon as possible, for they may act as an irritating factor, inciting attacks. It is necessary to keep epileptics in the best mental and physical health possible.

The treatment of epilepsy is mainly to prevent the occurrence of attacks, as very little can be done for individual attacks. Therefore, the preventive measures will be dealt with first.

### Preventive Treatment.

(a) **General.** — Epileptics, whether adults or children, should be taught to live as normal lives as possible. This means close co-operation and understanding among the physician, parent, teacher and employer. It is true that there are certain restrictions, but they are for the patient's own safety, and they still may lead fairly normal lives. An epileptic child may be allowed to play with other children as long as he does not become over-fatigued. He must go to school as other children, and be expected to do the same work. If he is backward or mentally defective, he should be placed in special classes, with work to suit his mental capacity. Parents and relatives are inclined to pamper and favour the child. They must be discouraged from doing this and advised to treat him as other children. However, the parents and teachers have to guard the child from excitement and fatigue, as these are incitants of attacks. There must be a regular routine followed by the child, including definite periods of play, school and rest. A well-regulated life is one safeguard against attacks.

As the epileptic grows up, the necessity arises for earning a living. He should be encouraged to find an occupation which he likes, and at the same time which will not be dangerous to himself or others, should he have an attack while at work. With treatment, many epileptics get along quite well and become useful citizens. The adult, as well as the child, needs to live a well-regulated life with definite hours for rest, recreation and work. Overwork and fatigue must be avoided.

Epileptics who have frequent attacks which do not respond to treatment, and those who live in unfavourable environments, with unintelligent relatives, are best treated in institutions or epileptic colonies.

(b) **Drug Treatment.**—At the present time, the one most reliable treatment for epilepsy is by the administration of drugs. There are two of these which are of the greatest value—bromides and luminal. Luminal is now replacing bromides to a large extent, but some cases are not benefitted by luminal, and here bromides are used. Luminal has little effect on petit mal, but frequently abolishes grand mal. Bromides usually, but not always, decrease petit mal attacks.

In using these drugs, it is essential to study carefully the periodicity of attacks in each patient, so as to obtain

the maximum benefit of the drugs when most needed. It is necessary to know how many attacks the patient has each day, and when they occur.

1. **Luminal.** — The dosage depends on the number of attacks per day. Patients who have attacks only occasionally do well on luminal gr. ½ to to gr. ¾ per day. Women who have attacks during menstrual periods should have gr. ½ per day. One week before the period is due, the dose is increased to gr. i., and reduced again to gr. ½ after the period is over. Patients with attacks occurring on rising in the morning or during the night get gr. i. before retiring. To those patients whose attacks occur frequently and at any time of the day, luminal gr. i. h.s. and a.m. is given. The dosage may need to be increased. When giving large doses of luminal, the patient is likely to be very drowsy during the day. This can be combatted by giving caffeine citrate gr. x. after breakfast and lunch, but not after the evening meal, as this would keep the patient awake.

2. **Bromides.** — Bromides affect the attacks of petit mal as well as grand mal. However, bromides cause reactions more frequently than luminal and hence are not used as much as formerly. But if luminal does not prevent the attacks, bromides have to be used or both together. They are used in the same way as luminal, being given before attacks. The dosage is potassium bromide gr. xv. to gr. xx. (or the equivalent of this in other salts), and not more than gr. lx. per day. In giving bromides, the NaCl intake is restricted in the diet, so that the bromide can replace the chlorine ion in the nervous tissue.

3. **Other Drugs.** — Atropine has also beneficial effects, especially in reducing petit mal attacks. It is frequently used together with bromides, and occasionally with luminal. This is also given before attacks, in doses of tincture of belladonna m. xv. to xx. per day.

Thyroid extract in small doses has, at times, been successful in cases of hypofunction of the thyroid gland or retarded development.

Corpus luteum hormone has also proven useful in women with attacks occurring near the menstrual periods.

(c) **Diet.**—It is necessary to have a generous, wholesome diet at all times. If the epileptic is undernourished when treatment is instituted, every effort should be made to build up the patient with a good bland diet, containing plenty of vitamins. Good nutrition has to be kept throughout the patient's life.

Certain diets have been worked out which in themselves limit the number of attacks. One of these is the ketogenic diet. The principle of this diet is to produce an acidosis which reduces the irritability of the nerve cells. This diet is very useful in children, but not in adults. The ketogenic diet consists of a diet high in fats and low in carbohydrates and protein. The amount of fat varies with the tolerance of the individual. Usually the ratio of fat: carbohydrate and protein is 2:1 to 4:1. This diet, however, is not tolerated well by many because of the high fat content. If adequate caloric requirements are maintained, this diet can be used for years in children under fifteen years. It is, however, extremely difficult to regulate such a diet in an ordinary household, and its use practically demands hospitalization.

Restriction of fluid intake is another dietary measure used. It is based on the theory that there is a hydration of the cerebral cortex producing the convulsions. The reduction of fluid lowers the fluid in the cortex and reduces the number of attacks. It is of great value in some cases.

As the biochemical changes in epilepsy come to be more clearly understood, dietary measures will doubtless assume greater importance in the treatment of epilepsy.

### Treatment of Attacks.

(a) **Epileptic Attack.**—There is no specific treatment for individual at-

tacks, and they are self-limited. The only thing one can do is to prevent the patient's injuring himself.

(b) **Status Epilepticus.**—This is a condition characterized by many epileptic attacks occurring in rapid succession. It often proves fatal and rigid treatment has to be instituted immediately. The convulsions can be stopped by giving morphine sulphate gr. ¼. Other things that can be used are paraldehyde oz. i.-ii. per os, or choral hydrate gr. lx. in oil per rectum. If the convulsions cannot be stopped, a general anaesthetic may be necessary.

After these preliminary measures, it is advisable to give colonic irrigations. Withdraway of spinal fluid has also been found useful. Dehydration can be combatted with intravenous saline. The patient should have sufficient sedatives to keep him drowsy for several days.

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# PARALYTIC ILEUS

By ALFRED AUERBACH, '38

Paralytic ileus is the term applied to a condition of paresis or paralysis of intestine. In this condition, there is a state of complete paralysis of part, or even all, the intestine, with the resultant accumulation of gas and toxic material in the lumen, distending the gut, interfering with the blood supply and resulting in a complete loss of muscle tone and absence of peristaltic movements. This results in an acute intestinal stasis with no organic block. The small intestine is most commonly involved.

## Etiology.

The cause of paralytic ileus is obscure. There is a nervous factor involved, also a toxaemia. The autonomic nervous system is involved, since its dysfunction may result in inhibition of intestinal tone and movements. Holt (B.M.L., May, 1936) says that inhibition of intestinal tone and movements is due to some injury of the neuro-muscular mechanism or else due to inhibitory impulses from spinal cord and coeliac plexus. The stimuli responsible for this interference with neuro-muscular function may be many and varied. A local lesion of the peritoneum or gut or injury elsewhere in the body—a fractured rib, or pneumonia—may cause reflex inhibition of the intestine.

The conditions in which paralytic ileus may occur are:

1. *Abdominal operations* are always followed by some paralytic ileus. Usually the condition passes off in a short period. In the first day or two following operation, the patient complains of "gas pains," due to the inco-ordinate spasmodic contractions of returning peristalsis—a sign looked for by the surgeon as indicating restoration of intestinal function. However, if the bowel is roughly handled at operation or else cooled by exposure to air, a serious type of paralytic ileus results.

2. *Peritonitis*, especially a diffuse or fibrino-purulent type or even a localized peritonitis or localized abscess. Ileus of the terminal loops of small bowel and a loop of pelvic colon occurs in pelvic inflammations. (Sampson Handley's "ileus duplex.")

3. *Biliary.*—Renal or ureteral stone or torsion of an ovarian cyst may produce reflex ileus.

4. *Mesenteric thrombosis* or embolism.

5. *Various conditions.* — Pulmonary infections (pneumonia), uraemia, chronic morphine poisoning, tabes, injury or tumour of spinal cord.

6. *Normal delivery* may rarely be followed by ileus.

### Clinical Features.

In the day or two following operation, there is a gradual distension of the abdomen, equal over the whole abdomen, but no associated pain. During the early stages, the intestinal musculature is still able to contract, but gradually loses this power as distension increases. The upper part of the abdomen becomes particularly full, due to the distension of the small intestine. There is no pain, although the patient suffers some discomfort, due to the distension. The patient may gag or hiccough and in a day or so begins to vomit. The vomiting is effortless, rolling out of the mouth over the face and chin. The color of the vomitus changes from green to black and faeculent as the case progresses, while the odour gradually becomes more foul. The temperature is subnormal, but may become elevated. The pulse is slow at first, later rising. There is absolute constipation.

In the terminal condition, the patient is tremendously distended, with great prostration and showing signs of toxicity. There is no tenderness, rigidity or visible peristalsis. On auscultation, no abdominal sounds can be heard. The facies usually show a sense of well-being and the patient says he feels fine. Death is the result of a number of factors, viz., absorption of toxic products, embarrassed intestinal circulation, loss of fluid and chloride in the vomitus, and upset acid-base equilibrium of the body. Examination of the bowel reveals marked distension of the walls, which are pallid and so thin as to be practically transparent.

### Treatment.

Paralytic ileus following operation is a very serious condition and must be guarded against. If there is danger of ileus occurring post-operatively, the following technique is employed:

1. Rest the intestinal tract, do not give cathartics or enemata.
2. No fluid by mouth, however, the mouth may be moistened by mouth wash or a dampened cloth put on the lips.
3. Give normal saline by continuour drip, regulating the amount by the urinary output, which should be at least 1000 c.c. daily.

If ileus actually occurs, the treatment is as follows (and usually in the order given) in any case of paralytic ileus:

1. *B. Welchii Serum.*—This should be given early in any case where peritonitis is a possible complication and should be repeated daily. 20 c.c. are given intramuscularly or intravenously. The serum is given to reduce the formation of the gas in the intestine.

2. *Eserine (physostigmine).* — 1/30 grain hypodermically every four hours. stimulates the parasym pathetic nervous system.

3. *Duodenal Flatus Tube.*—This is a suction arrangement, whereby the stomach is kept empty of fluid and gas which has been regurgitated from the intestine, promptly relieving the vomiting.

4. *Hypertonic Saline.*—By mouth or intravenously, 600 c.c. of 6% solution increases the irritability of the neuromuscular junction, resulting in peristalsis. Intravenous hypertonic saline is followed by administration of normal saline, often producing most dramatic effects.

5. *High Spinal Anaesthetic.* — Produces paralysis of the reflex arc through which the inhibitory fibres pass.

Other forms of treatment which may be tried, although not always efficacious, are:

6. *Acetyl Choline.* — 1/10 gram hourly. 5-6 doses.

7. *Pituitrin.*—(See below).

8. *Radiant Heat or Poultices* to abdomen.

The use of morphine or any surgical interference is contra-indicated. Enterostomy, when attempted, has resulted in 85% mortality.

In any case where there is associated peritonitis, treat by placing pa-

tient in Fowler's position and giving heat and intravenous saline.

Potter reports on the use of pitressin at Bellevue Hospital, New York. In 23 deaths, due to diffuse or fibrinopurulent peritonitis following appendicitis, 16 cases could be proven due wholly or partially to paralytic ileus. Since pitressin has been put to routine use in the hospital, only two deaths due to peritonitis have occurred, but neither showed any indication of ileus. In a series of 550 abdominal operations, in which pitressin was injected intramuscularly at beginning of operation, not one showed paralytic ileus. Potter advocates prophylactic use of pitressin at beginning of abdominal operation, followed by 8-10 doses during post-operative care, dosage depending on case. No cathartics or enemata are to be given until pitressin is stopped.

### Prognosis.

If patient survives for a week, the prognosis is good.

### Differential Diagnosis

(a) *Post-operative Haemorrhage.*— More rapid pulse, restlessness and air-hunger, abdomen is acutely tender on pressure and shows shifting dulness. Absence of distension and vomiting.

(b) *Intestinal obstruction, due to mechanical causes. — Cramping pain,* projectile vomiting, visible peristalsis.

The diagnosis of paralytic ileus depends on appearance of abdominal distension in a few days usually following operation: absence of pain, tenderness and rigidity, followed by effortless vomiting.

The author wishes to thank Dr. Ross and Dr. Couch for their kind assistance.

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# TISSUE CULTURE

By W. H. PERRY, '39, and D. H. COPP, B.A., '39.

## Introduction.

Tissue Culture is a technique of relatively recent development, yet in its short twenty-five years of existence, it has proven itself of great value in almost every branch of medical science. Indeed, it is considered by many as the most important biological method which has come into use during this century. Every medical student has heard of it in his studies of Histology and Pathology, but to most the technique is still shrouded in mystery. The purpose of this article is to outline the method in its simplest essentials and to present some of its contributions to the advancement of medical knowledge.

## Historical.

Thirty years ago, the microscopic study of the cells and tissues of the body was almost entirely limited to dead stained sections. Little could be learned of the dynamics of the living cell from these static preparations. True, unicellular organisms like the amoeba were used for investigation, but results obtained with these could hardly be considered applicable to human cells.

At the end of the last century attempts were made to keep fragments of tissue from higher animals alive outside the body. The first difficulty experienced was overgrowth of the tissue by bacteria. This was to be expected, for the tissues were necessarily separated from the defense mechanism of the body. This obstacle was overcome by the maintenance of strict asepsis in every step. Moreover, cells in the body, unlike the amoeba, exist in a complex and delicately balanced medium, in which even small variations may prove fatal to the cell. Various physiological solutions, such as dilute sea water and Tyrode Solution were tried with disappointing results. Obviously, blood serum or tissue fluid, such as bathes the living cells in vivo (i.e., in the body), would seem to be the most suitable medium. Harrison, in 1907, following this theory, cultured frog nerve cells in frog lymph and actually observed nerve regeneration outside the body. This was the first practical tissue culture and its first real contribution to medical science. It was followed by attempts to grow mammallian tissues in serum, but the results were very unsatisfactory, as the cells soon rounded up and died.

Loeb postulated that some supporting framework was necessary for cells living in vitro (i.e., outside the body), just as cells in the body received support from those adjacent and from the fibrous stroma. Burrows and Carrel, keeping this in mind, grew tissues in a drop of clotted blood plasma (blood from which the cells have been centrifuged off). The threads of the fibrin network in the clot provided an excellent frame work along which the cells wandered. Moreover, the fibrin had the added advantage of being transparent, so that it did not interfere with observations. These cultures lived for a few days, but then degenerated, due to the accumulation of waste products and exhaustion of the food supply. This disadvantage was overcome by removing the tissue from the culture every few days, washing, and implanting in a fresh medium.

When continually subcultured in this manner, the tissue survived for two or three months. However, there was no increase in bulk of the tissue—that is, there was no true growth. In an attempt to produce such growth, Carrel prepared a saline extract of the very rapidly growing tissues of a chick embryo and added this to his cultures of embryo chick heart A luxuriant pro-

liferation of heart fibroblasts was obtained. The addition of this "embryonic extract" had produced true growth—with active cell division and increase in mass. Carrel's original culture of fibroblasts has never ceased to proliferate through repeated subcultures and now, at the ripe old age of twenty-five years, is safely ensconced in the Rockefeller Institute as hail and hearty as the day it nestled comfortably in the egg. Fortunately, it was carefully pruned on sucessive tranferrs or its bulk would now be many times that of the earth. This procedure proved so successful that, with modifications, it has been the basis of most subsequent methods of tissue culture.

**Technique.**

(a) *Hanging Drop*—

This technique, first developed as outlined above, is still the most widely used and is the method employed in the Tissue Culture Laboratories at Toronto.

In its simplest form, a fragment of living tissue, generally less than one millimetre in diameter, is placed in a drop of medium on a cover-slip, which is then inverted over a hollow-ground microscope slide and sealed off with vaseline or paraffin-wax before being placed in an incubator to maintain the tissue at the normal temperature of the animal's body The medium generally contains plasma which sets in a solid fibrin clot, providing a framework on which the cells may grow. Embryonic extract is often added, particularly when growth, especially of connective tissue, is desired.

The technique has certain advantages in studying the phenomenon of growth:

1. Pure tissue strains may be isolated and grown.
2. The living cultures may be observed continuously under the microscope, and the rate of growth roughly measured.
3. The culture medium may be carefully controlled.

There are also certain drawbacks, which must be considered:

1. The tissue is not strictly in its normal environment.
2. There is not the normal exchange of food and waste products between the tissue fluids and the blood, so that their concentrations must alter with time.
3. The amount of medium is small, so that slight evaporation changes the concentration, and food and oxygen is soon exhausted. This disadvantage is overcome to a large extent by the next method, where the volume of medium is large and may be easily renewed.

(b) *Carrel Flask*—

The essential apparatus is the Carrel flask, so called after its inventor. It consists of a small flask, 3-5 cms. in diameter, flat at the top and bottom, like a Petri dish, and with a neck at one side, slanting obliquely up for introducing the materials. The tissues are grown in a thin layer of coagulated blood plasma (about 1 mm. thick) on the bottom of this flask. The solid coagulum is covered by the fluid medium, which may be changed every few days, thus washing and refeeding the cultures without disturbing them. The greater quantity of medium tends to prevent great changes in composition. The chief drawback is the difficulty in observing the cultures, due to the thickness of the flask. Microscopes placed upside down have been used, but such an arrangement is, to say the least, inconvenient. However, low-power observations may be made and are quite satisfactory for following increases in the area of the tissues and growth of the cultures.

(c) *Carrel-Lindberg Method of Culture of Whole Organs*—

This technique—a logical development of tissue culture methods—bridges the gap between the cultivation of minute tissue fragments and physiological perfusion. This procedure

was made possible by the use of the ingenious "mechanical heart," devised by Col. C. A. Lindberg, which pumps a pulsating stream of sterile perfusing fluid through the vascular system of the organ, under strictly aseptic conditions.

The thyriod, ovary and several other organs have been kept alive and healthy for several months by this method. The thyroid continued to produce thyroxin and even showed signs of hyperplasia. The opportunities for this technique are almost unlimited and promise to produce revolutionary advances in physiology, particularly in the endocrine field.

## Physiology.

Tissue culture has contributed a great deal to the study of cellular physiology. It has afforded the first opportunity for investigations on pure strains of living cells segregated from other tissues of the body. Naturally, much of the interest has centered around the growth of cells in vitro, for in the early experiments, this was the most prominent feature.

The laws of growth in the body are not well understood. In general, most cells of the adult body, in contact with normal tissue fluid, do not exhibit growth. Similarly, it was found that cells of cultures repeatedly fed with plasma, will survive for long periods, but will not proliferate. Apparently in both cases the cells are able to obtain food for life from the serum bathing them, but not material for synthesis of new protoplasm. Under certain conditions, however, active growth does occur, as in the developing embryo, in repair and in tumours. There are also the proliferate changes of the uterus and breast with pregnancy and during the menstrual cycle, which may be due to the effect of the sex hormones acting on the cells. Such growth may be obtained in vitro by adding embryo extract to the cultures. The hypothetical substances in the extract responsible for this growth have been rather loosely named "trephones" or cell feeders. It is not yet known whether these substances act as direct growth stimulants, or by providing material for building new protoplasm, or both. Such activity has also been found in extracts of adult spleen, leucocytes and Rous sarcomata. It is interesting to note that application of embryo extract to a wound produces much more rapid healing and repair, so that the effect is not limited to tissue cultures alone.

Fischer analyzed the extract in order to determine the substances responsible for its activity and concluded that it was probably due to heat labile compounds associated with the globulin fraction. It is unlikely that the nitrogenous food material of this fraction is chiefly responsible for its potency because serum contains far larger amounts of globulin, and yet is inert. It is more probable that it acts directly on the cell.

Investigations followed on the effect of various nitrogenous substances which might be used for protoplasm synthesis. Amino acids and proteins had no effect, but proteoses and other higher split protein products produced tremendous proliferation for a short time. This effect was only transitory and wore off in a few days unless a trace of embryo extract was added. When this was done, the growth continued for long periods and was far greater than that caused by a similar quantity of extract alone. Apparently proteoses form the ideal source of protein nitrogen for synthesis of new protoplasm, but some factor contained in embryo extract is also necessary if the growth is to continue. If the nature and action of these factors were clearly understood, it would greatly clarify our ideas of growth, repair and neoplasm.

Interesting work has also been done in the endocrine field. Lewis and Geiling have observed actual production of epinephrine by the epithelium of the adrenal medulla. Similar results have been obtained with thyroid and pituitary tissue. The influences of hormones

on pure cell strains isolated from the influences of the body may also be investigated. For example, the effect of the female sex hormone, oestrin, on uterus or breast epithelium in vitro might be studied, to determine if its action is one of stimulating cell growth directly.

Even in the more conventional fields of physiology, such as kidney function, tissue culture has a place. Chambers cultured kidney tubules of the chick in vitro, separated from the glomeruli, and was able to show that the tubules excreted certain dyes into their lumina, against a high concentration. This was convincing evidence of the excretory power of the tubular epithelium, once thought to have only the power of re-absorption.

## Histology.

The advantage of tissue culture as an aid to the understanding of histology is evident, for it allows continuous observation of living cells under the microscope. Particularly useful in this respect are motion pictures of such cells in culture, taken at intervals of a few minutes and speeded up on the screen, so that the changes in the cells may be easily followed. Such a movie of chick heart fibroblasts, exhibited at Toronto some years ago, showed beautifully the cellular activity, the streaming cytoplasm, the motile mitochondria, and at intervals the violent changes of mitosis and cell division. To view it was to gain a new conception of the cell as a very active body, rather than as the conventional stained structure seen in fixed preparations.

Tissue culture has also laid emphasis anew on the dependence of the cell upon its environment. We have already seen that the spindle-shaped fibroblasts, if left in a fluid medium with no support, soon round up and later degenerate and die. Similarly, fibroblasts growing on the surface of the clot sometimes appear like epithelium. These changes in morphology are not permanent and depend only on the conditions of the environment.

Again, the presence of embryo extract leads to marked unorganized proliferation not unlike that seen in some tumours of the body. When no such growth stimulant is present, the tissues tend to differentiate. Indeed, in tissue cultures, it has been found that growth and differentiation of cells are entirely separate, if not opposing processes, which do not tend to occur simultaneously.

Gaillard grew tissue of a very young chick from the region which later develops into the frontal bone. He embedded the fragments in a fibrin clot, which had been washed free of adult serum. These cultures were divided into two groups. The control group was fed with extracts of embryos of the same age as that from which the tissue was obtained. The experimental group was fed with extracts of successively older embryos and later with the blood of newly hatched chicks. In the controls, there was no differentiation observed. The experimental cultures, however, as progressively older extracts were used, showed differentiation of the primitive mesenchymal cells into osteoblasts, and, finally, bone formation took place. Apparently the age of the animals from which the extract, and later the blood, was obtained, influenced the differentiation of the primitive tissue into bone.

The effect of neural organizers, prepared by ether extraction of the neural tissues of very young embryos, has also been investigated. These substances, when applied to the ectoderm of cultured embryos of twenty-four hours, induce the formation of a new neural tube in this region, and may even lead to the formation of twin monsters. Here again some external factor has directed cell differentiation.

A third very important factor in the environment is the close proximity of other cells and tissues. Pure strains of both epithelium and fibroblasts from embryo chick intestine were isolated and grown separately in culture. Both were maintained in an active state of growth without differentiation. When

these two strains were cultured together, however, they combined to form definite little growths in which the structure of the normal intestine began to make its appearance. The epithelial cells formed membranes around the mesenchyme cells and developed crypt-like structures with typical glandular cells. It is probable that such interrelationship of tissues plays a very important part in the formation of the organs of the body.

## Pathology.

In the last few years, tissue culture has been extensively applied to the study of pathology. It is probable that the future will see its use extended, for it offers an excellent method of studying the action of abnormal influences on pure strains of both normal and abnormal tissues isolated from other complicating factors.

Tumours, in particular, offer a very fertile field for such investigations. Sarcomata have been most widely studied, due to the ease with which they may be cultured, although considerable work has also been done on breast cancers. The continued malignancy of these tumour cultures has been confirmed by re-implanting in the body. Just as in vivo, there are all gradations between normal and malignant cells. So in vitro it is difficult to give characteristics applicable to all types of tumours. However, in cultures of the more malignant tissues, such as the Rous chicken sarcoma, three essential departures from the normal have been noted:

1. The cells are able to grow and synthesize new protoplasm from serum alone without the presence of embryo extract.
2. The cultures soon liquefy the fibrin clot, suggesting the active production of proteolytic enzymes. If normal tissue is present, it will also be dissolved.
3. A single sarcoma cell may live, grow and divide, even when completely isolated from the other cells, in contradistinction to normal connective tissue cells which grow as a syncytium and die if separated from one another.

These characteristics may explain the uncontrolled growth, destructive power and metastasis of a malignant tumour in the body.

The very vital problem of the production of tumours has also been studied in cultures, but the work has been very meagre, so that no definite conclusions should be drawn. Fischer and Laser, by adding arsenic to cultures of chick spleen, observed the transformation of normal fibroblasts into sarcomo cells, as evidenced by their malignancy when implanted into animals. Laser reported a similar result after irritating growing fibroblasts with tar. The action of the pure carcinogenic compounds—first isolated from tar—has also been studied in vitro. Kendall suggests that they slowly alter the cells in such a way that they can afterwards live and proliferate on serum alone, in contrast to normal cells which require embryo extract or its equivalent. This would be one factor in producing malignancy. Hearne observed irregular mitosis and chiasma formation in cultures treated with these compounds, again showing a change to a more atypical cell.

The effect of irradiation on cells in culture has been the subject of considerable study in an attempt to understand its function in the treatment of tumours. Cox and Love have stressed the fact that the cell is most sensitive to X-rays in the short premitotic phase. Hence the rapidly dividing tumour cells are much more easily destroyed by this treatment than the resting normal cells. Again, a relatively weak dose administered continuously for a long period will be more effective than a single, large, short dose, since the former will catch many more cells in the sensitive premitotic phase.

Inflammation is another field to which the technique has been applied.

Indeed, the formation of granulation tissue, and the invasion of a blood clot or fibrinous exudate by fibroblasts bear a striking resemblance to tissue cultures. A few of the conclusions reached on the evidence from tissue cultures are tabulated below. These must be accepted with some reservations due to the limitations of the technique:

1. Polymorphonuclear leucocytes are fully differentiated cells.
2. Monocytes, large and small lymphocytes may be progressively converted into polyblasts, histiocytes and finally into fibroblasts. This would suggest that granulation tissue need not be entirely formed from the pre-existing connective tissues.
3. The normal vascular endothelium has no haematopoietic function in inflammation. This is in opposition to Mallory's view.
4. There is a possibility that undifferentiated mesenchymal cells may occur in the tissue and retain their full cytopoietic potency.
5. Alveolar phagocytes in culture are in every respect morphologically and functionally identical with macrophages. There is no evidence that they may arise from vascular endothelium. In cultures of lung tissue, no alveolar epithelial lining was discovered.
6. The epithelioid cells of tubercles are hypertrophied macrophages.

Other interesting experiments on granulomatous reactions have been performed. Dr. Franks has observed the active phagocytosis of silica particles by macrophages, and found that when the cells became engorged, they lost their motility. This confirms the pathological findings in silicosis. Many workers inoculated cultures of lung or lymphoid tissue with B. tuberculosis. Provided no subcultures are made, a characteristic reaction is obtained—aggregation of macrophages, formation of epitheliod and giant cells, and sometimes even caseation. This technique should provide an opportunity for studying the cellular response in inflammation uncomplicated by the vascular reaction.

In bacteriology, tissue culture holds much promise of usefulness in the virus field, for the existence of the latter is closely bound up with that of the living cell. Already many types of viruses have been grown by this method. Parker and Nye inoculated flask cultures of embryo chick tissue with smallpox virus and in eight days found that the amount had increased four hundred times. These figures indicate that a cultured chick embryo can produce as much virus as a calf. This may prove a valuable method of producing viruses in the future. Other viruses that have been similarly cultured are herpes, coryza, Manchurian typhus, yellow fever, etc. All of them have shown a great increase in amount or "growth."

## Conclusion.

This necessarily sketchy outline is only intended to give a general idea of the methods and scope of tissue culture, in the hope that it may help the student to appreciate better the results obtained from this technique, and the opportunities which it offers for future investigations in the biological and medical sciences.

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# THE DEVELOPMENT OF THE HUMAN GASTRO-INTESTINAL TRACT.

By J. H. BELTON, '39

In the beginning, the embryo was just a small disc of cells forming the bottom of one bag of fluid and the roof of another. The upper bag, or amnion, was protective, while the lower, or yolk sac, was nutritive in nature. Soon this embryonic disc differentiated into three germ layers of ectoderm, mesoderm and endoderm, leading to the definition of the splanchopleure. The ventrally growing splanchopleure growing towards its fellow of the opposide side, pinched off the upper portion of the yolk sac and the primitive gut was formed.

Due to its steady growth, the embryo bulged into the amniotic sac, which continually enlarged to accommodate its charge. As the amnion enlarged, it did so at the expense of the yolk sac, which decreased in size until it became just a small bag joined to the ventral aspect of the embryo by the yolk stalk. The primitive gut was, therefore, just a straight tube slung in the mid-line by a ventral and dorsal mesentery. This tube was closed at either end, but connected at its middle to the yolk sac.

In the primitive gut, *three divisions may be recognized:*

1. Fore-gut, which gives rise to the gastro-intestinal tract as far as the opening of the Ampulla of Vater into the duodeum. Its artery of supply is the coeliac axis and its function is, roughly, digestive.

2. Mid-gut, which gives rise to the remainder of the small intestine and the large intestine down to the junction of middle and left thirds of the transverse colon. Its artery of supply is the superior mesenteric and its function, roughly, absorption.

3. Hind-gut, which is the remainder of the gastro-intestinal canal down to the pectinate line of the anal canal. Its artery of supply is the inferior mesenteric and its function, roughly, excretory.

Since the digestive tube is slung from the dorsal body wall by a mesentery, it and its vessels of supply will always lie anterior to any structure, and its vessels, which develop in the posterior body wall. Thus the duodenum is in front of the kidney and the superior and inferior mesenteric arteries are in front of the renal and gonadic vessels.

### The Development of the Fore-Gut.

The fore-gut ends blindly at its cranial end. An invagination of the overlying epithelium soon appears, called the stomadeum, which forms the primitive mouth. The stomadeum is separated from the fore-gut by the pharyngeal membrane, which breaks down, establishing communication between gut and mouth. The cranial portion of the fore-gut gives rise to the branchial arches. From the caudal and ventral aspect of the pharynx buds out the primitive lung. The fact that it lies ventral to the digestive tube may help one to remember the relative positions of the phrenic and left vagus nerves just above the aortic arch.

*The Oesophagus.* — At first, the oesophagus is a mere stricture between the pharynx and stomach, forming a single structure with the trachea. Invaginations of the lateral walls of this structure divide it into trachea anteriorly and oesophagus posteriorly. If the splitting is not complete, an oesophago-tracheal fistula occurs, in which there is a communication between the oesophagus and trachea, commonly in the lower part. The growth of the lung buds and the heart push the stomach caudally leading to elongation of the oesophagus.

*The Stomach.*—The first appearance of this organ is a spindle-shaped enlargement slung in the mid-line by a dorsal and ventral mesogastrium. The dorsal border of the enlargement grows faster than the ventral, forming a convex greater curvature and a concave lesser curvature. The fundus is a local bulge at the cranial end. At this stage, the primitive stomach is just a dilated portion of the tube to the right and left surfaces, of which the respective vagi are distributed. An invagination begins to form in the dorsal mesogastrium, pushing towards the left, and this in time becomes the omental bursa.

Coincident with the formation of the stomach is the budding of the liver from the ventral aspect of the duodenum. The liver rapidly fills the upper right portion of the abdomen, displacing the stomach from its mid-line position and shoving the upper end of the stomach to the left and the lower end passes to the right. At the same time, it causes rotation of the stomach through ninety degrees in an anticlockwise direction, so that the former right surface faces posteriorly and the left surface anteriorly. Thus the left vagus is distributed to the anterior surface of the stomach and the right vagus to the posterior surface and the omental bursa comes to lie behind the stomach.

*The Liver.* — While the mid-line stomach is just beginning to form, a small diverticulum buds out from the ventral aspect of the primitive duodenum. This hepatic diverticulum gives rise to the liver, gall bladder, head of pancreas and their ducts. More than one diverticulum may bud out from the ventral surface, but usually they disappear. If not, the adult duodenum may exhibit multiple diverticula. It plunges into the ventral mesentery and gives off a bud which forms the head of the pancreas and another bud which forms the gall bladder. It then divides into right and left hepatic ducts which continually branch and rebranch, forming numrous little test tube-like buds called hepatic cylinders. These cylinders invade the anastomosing branches of the vitelline and umbilical veins, which are running through the septum transversum and carry the endothelial walls of the vessels before them. This divides the veins up into sinusoids which run between the hepatic cylinders. The mesenchymal tissue of the septum transversum forms the connective tissue and capsule of the liver. As the liver enlarges, it projects downwards and divides the ventral mesentery into two parts, the anterior part forming the falciform and coronary ligaments and the posterior the lesser omentum. The ventral mesentery disappears beyond the point of the hepatic diverticulum and hence the lesser omentum becomes the omentum of the common bile duct. By the third month, the liver nearly fills the abdominal cavity, when its relative development slows down, but even at birth, the liver is relatively larger than in the adult.

*The Pancreas.* — The pancreas develops in two parts—(1) from the common bud into the ventral mesentery with the hepatic diverticulm. (2) From a bud from the dorsal surface of the duodenum into the dorsal mesentery.

The head of the pancreas and its main duct arise from the ventral outgrowth, while the neck, body, tail and accessory duct, if present, arise from the dorsal outgrowth. The dorsal outgrowth causes the duodenum to arch ventrally. The reason for the main duct of the pancreas and the common bile duct opening into the Ampulla of Vater together is plain, if the developmental story is remembered.

Unequal growth in the walls of the duodenum causes twisting, which drags the ventral pancreatic outgrowth and the common bile duct around behind the duodenum. Thus the ampulla, instead of emptying into the ventral aspect of the duodenum, empties into its postero-medial aspect, and the posterior relation of the common bile duct to the first part of the duodenum is explained. The synchronous rotation of the stomach aids the rotation of the duodenum and the duodenum passes towards the right from its former mid-

line position. When this occurs, the dorsal outgrowth is thrown in front of the superior mesenteric vessels and the ventral outgrowth swings around behind, so the two portions of the pancreas close like pinchers on these vessels. As the pancreas is shoved against the posterior body wall, its mesentery is absorbed and the pancreas becomes retroperitoneal. Usually an anastomotic duct joins the upper pancreatic duct to the lower and the opening of the upper duct into the duodenum closes off. If this upper duct does not close, it forms an accessory duct of Santorini, which necessarily empties separately into the duodenum and not into the ampulla of Vater.

**The Development of the Mid-Gut.**

Early in development, the mid-gut is widely open to the yolk sac by the vitello-intestinal canal. This opening becomes smaller and smaller until it is just a duct running from the mid-gut through the abdominal cavity to the remnant of the yolk sac left in the umbilical cord. Normally, this vitello-intestinal duct disappears in the whole of its extent from intestine to umbilicus, but various portions of it may remain. In 2% of the people, the proximal intra-abdominal portion persists as Meckel's diverticulum averaging 2 inches in length and situated two feel from the ileocaecal valve. Since it is a vestigal structure, its tissues are prone to metaplasia, resulting sometimes in active glands of the gastric type.

When the mid-gut begins its growth, it is just a mid-line tube slung by a dorsal mesentery, through which runs the superior mesenteric artery. This artery runs directly to the central portion of the mid-gut, where the vitello-intestinal duct comes off, and thus form the axis of the mid-gut. Continuous elongation of the mid-gut gives rise to a U-shaped loop hanging in the mid-line, which may be described as having prearterial and postarterial limbs with respect to the axial artery. The ends of the loop are fixed. The cranial end is fixed at the duodenum in the region of the hepatic and pancreatic diverticula and the caudal end is fixed at the colic angle, where hind and mid-gut meet. These points of fixation are close together in the mid-line, being separated by a narrow space called the duodeno-colic isthmus, through which runs the superior mesenteric artery.

The continuous enlargement of the liver and gut so increases the pressure in the coelomic cavity that the growing gut is squeezed out into the umbilical cord. The two loops are tightly packed in the cord with the superior mesenteric artery between running out to the vitello-intestinal duct at the apex. This physiological hernia occurs between the fifth and tenth weeks.

"Stage of Rotation."—The steady growth of the liver pressing upon the pre-arterial loop causes it to rotate through 90 degrees in an anticlockwise direction. Due to the cramped quarters of the gut in the umbilical cord, the postarterial loop necessarily rotates 90 degrees in an anticlockwise direction also, because of the movement of the pre-arterial loop. The final result is that the gut, instead of lying in the sagittal plane in the umbilical cord, is rotated so that it lies on a transverse plane, the pre-arterial limb being to the right and the postarterial limb to the left of the axial artery. Preceding this phase, a small bud appears on the postarterial limb a little caudal to the vitello-intestinal duct. This caecal bud marks the junction of small and large intestine and grows until it attains the largest circumference of the intestinal canal.

"Stage of Reduction."—Soon the gut begins to return to the coelomic cavity, reducing the physiological hernia. It is believed that the coelomic cavity has enlarged sufficiently to reduce the pressure upon its contents and the gut returns to the region of lower pressure. The reduction is carried out in an orderly manner The pre-arterial limb reduces first because it is thought that the caecal bud on the postarterial limb keeps the latter stuck in the um-

bilical cord until the pre-arterial limb is reduced. The pre-arterial loop passes up and to the right, due to its transverse position in the umbilical cord. Because of the large bulk of the liver, this space is soon filled, and thus the following gut passes towards the left. The superior mesenteric artery running from the aorta to the apex of the gut in the cord is held taut by its connections and the gut passing towards the left passes behind the artery. This explains the relation of the superior mesenteric vessels to the third part of the duodenum. As the gut passes towards the left, it pushes the colic angle before it, displacing it from the midline up and to the left, where it forms the splenic flexure. The pre-arterial loop thus fills up the central portion of the abdominal cavity, so when the post-arterial loop reduces, the only space left is around the margins of the pre-arterial loop. The caecal bud and ascending colon reduce into the right flank and the transverse colon passes across the abdomen anterior to the duodenum to its point of fixation at the splenic angle. Thus the large gut forms three-quarters of a picture frame around the small gut. The gut cannot be coiled upon itself, due to the necessity of preserving the integrity of its blood supply, hence the retention of the pre-arterial portion of the mesentery to convey the arteries.

"Stage of Fixation." — From the eleventh week until just after birth, the fixation of the gut to the posterior abdominal wall occurs. At the end of reduction, the gut has practically reached its permanent position, except in the case of the caecum.

Whenever gut is pushed up against the posterior body wall, the visceral and parietal peritoneum fuse and disappear, thereby fixing the gut. The duodenum, caecum, ascending colon, hepatic flexure and hind-gut, with the exception of the pelvic colon, lose their mesentery in this manner. Their dorsal mesentery, except in the case of the transverse colon, is not needed to convey blood vessels, so it disappears. The caecum at first lies under the liver, but due to the growth of the posterior abdominal wall and the elongation of the ascending colon, the caecum descends into the right iliac fossa. Position of the caecum depends upon its time of fixation. If the fixation occurs early, it may remain subhepatic or right lumbar. If it occurs late, the caecum may reach the pelvic position.

Various positions of the appendix may also be explained upon developmental grounds. The caecal bud appears on the postarterial loop of the gut. At first, the diameter of the bud is the same size throughout, but soon its tip lags in growth and so forms the appendix. A relative increase in growth of the right wall of the caecum shoves the appendix around towards the left, so it appears to be budding out from the left wall. Dependent upon the degree of growth of the right wall of the caecum, the appendix may vary in position from where it points down to the iliac fossa in line with the caecum to a retro-ileal or retro-caecal position.

**The Development of the Hind-Gut.**

Early in development, the hind-gut ends blindly near the surface of the perineum. An invagination of the skin overlying it occurs, producing the proctodeum, but the gut and the proctodeum are separated by the cloacal membrane. This distal portion of the gut is called a cloaca, i.e., sewer, as the developing kidneys are connected to its anterior portion. From the side walls of the cloaca, transverse ingrowths fuse with each other, forming the recto-vesical septum. This septum divides the cloaca into an anterior uro-genital portion and a posterior rectal portion. If development is faulty, a recto-vaginal fistula may occur. The cloacal membrane overlying the rectal portion breaks down, establishing communication with the exterior.

In the anal canal the line of junction between hind-gut and proctodeum is represented by a wavy white line—the pectinate or Hilton's line. As might be expected from the develop-

mental story, the nervous and vascular supply of the gut differs on each side of the line. The gut above is supplied by the sympathetic nervous system. The gut below by the cerebro-spinal nerves. The inferior mesenteric artery supplies the gut above. the internal pudendal that below. The gut above is drained by the portal system, that below by the systemic system. The lymph from the gut above drains to the pelvic lymph glands, while the superficial inguinal glands receive the lymph from the anal canal below.

Following the displacement of the colic angle up into the left flank, the mesentery of the hind-gut disappears except in case of the pelvic colon and the hind-gut is fixed in its permanent position.

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# MEDICAL INSTRUCTION AT THE UNIVERSTY OF FRANKFURT.

By MARIA EMBDEN,
Frankfurt-on-Main.

The German medical student enters the Faculty of Medicine of Frankfurt University at the age of 18 or 19, after matriculating from high school and working half a year in a working camp.

The pre-clinical work lasts 2½ years and includes Biology, Chemistry, Physics, Anatomy, Biochemistry, and Physiology. Examination in each of these subjects then takes place, and after passing, the student changes his title from "medical student" to "medical candidate."

Clinical work extends over three years and includes Pathology, Pharmacology, Hygiene, Medicine and Surgery. During the semester, we must spend almost all day in lectures and laboratories, leaving hardly any time for practical work on the ward. The clinical teachers in Frankfurt present many patients in these lectures, especially Professor Volhard, the internist, who never lectures without bringing in some cases, most often of heart and kidney disease. During the lecture he has some of the students examine them before the others.

The surgery lecture hall is a modern operating room in itself and Professor Schmieden, Head of Surgery, demonstrates the most important types of operations two or three times a month. In addition to general surgery, Frankfurt University has a special orthopaedic department in a more modern building, founded by private donations. The head of this department, Professor Hohmann, and his staff, composed of assistant surgeons, masseurs and masseuses, teach physiotherapy in courses 1½ years long. Once a week, cripples come from the province for examination and treatment. Professor Hohmann himself very often goes out into the country and holds clinics. He is most interested in very young children, because the chances of success in treatment are much greater, the earlier it is instituted, especially in luxatio coxae, club-foot and flat-foot. Frankfurt and the surrounding country have very many cases of luxatio coxae, in contrast to the rest of Germany, where one finds hardly any. Treatment for this disease requires about one year, with a very high percentage of complete cures. The gymnastics are done with the least possible amount of apparatus, and the exercises for orthopaedic cases are kept so simple that, on discharge, the patients can continue them at home. In addition to ordinary massage, massage under water is often

applied and soon a heated swimming pool will be built especially for the use of patients recovering from infantile paralysis. All patients in Frankfurt suffering from this disease are treated in the Orthopaedic Hospital.

The practical work of the students is nearly all done in the long vacations (4½ months in summer; 1½ months in winter). During the past few years, all the girls do quite a bit of nursing in surgery, mostly before beginning their summer internship.

Following the three years' clinical work, the oral state examinations take place. Two weeks later, one begins a compulsory internship, of which four months must be spent in a general hospital. The other eight months, one may work wherever one pleases, for example, in a pathology laboratory. At the end of this year, the student recieves his M.D., if he passes an examination, which is usually rather easy, and his thesis is accepted.

**WHAT EVERY WOMAN DOESN'T KNOW —HOW TO GIVE COD LIVER OIL.**

Some authorities recommend that cod liver oil be given in the morning and at bedtime when the stomach is empty, while others prefer to give it after meals in order not to retard gastric secretion. If the mother will place the very young baby on her lap and hold the child's mouth open by gently pressing the cheeks together between her thumb and fingers while she administers the oil, all of it will be taken. The infant soon becomes accustomed to taking the oil without having its mouth held open. It is most important that the mother administer the oil in a matter-of-fact manner, without apology or expression of sympathy.

If given cold, cod liver oil has little taste, for the cold tends to paralyze momentarily the gustatory nerves. As any "taste" is largely a metallic one from the silver or silverplated spoon (particularly if the plating is worn), a glass spoon has an advantage.

On account of its higher potency in Vitamins A and D, Mead's Cod Liver Oil Fortified With Percomorph Liver Oil may be given in one-third the ordinary cod liver oil dosage, and is particularly desirable in cases of fat intolerance.

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